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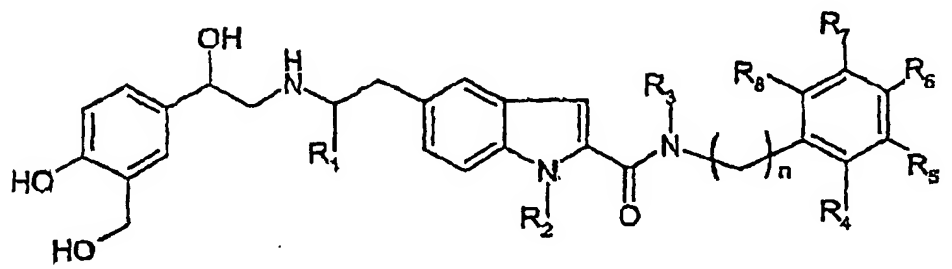
(54) Title: INDOLE DERIVATIVES AS BETA-2 AGONISTS



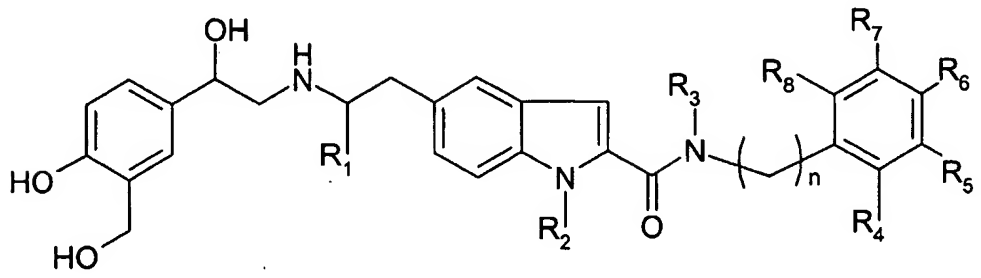
(1)

(57) Abstract: The invention relates to indole derivatives of formula (1), wherein R_1 to R_8 and n have the meanings given in claim 1 to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives. The indole derivatives according to the present invention are useful in numerous diseases, disorders and conditions, in particular inflammatory, allergic and respiratory diseases, disorders and conditions.

WO 2004/032921 A1

INDOLE DERIVATIVES AS BETA-2 AGONISTS

This invention relates to β2 agonists of the indole derivatives family of general formula :



(1)

in which R_1, R_2, R_3, R_4 R_5, R_6, R_7, R_8 and n have the meanings indicated below,

and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

Adrenoceptors are members of the large G-protein coupled receptor super-family. The adrenoceptor subfamily is itself divided into the α and β subfamilies with the β sub-family being composed of at least 3 receptor sub-types: β1, β2 and β3. These receptors exhibit differential expression patterns in tissues of various systems and organs of mammals. β2 adrenergic (β2) receptors are mainly expressed in smooth muscle cells (e.g. vascular, bronchial, uterine or intestinal smooth muscles), whereas β3 adrenergic receptors are mainly expressed in fat tissues (therefore β3 agonists could potentially be useful in the treatment of obesity and diabetes) and β1 adrenergic receptors are mainly expressed in cardiac tissues (therefore β1 agonists are mainly used as cardiac stimulants).

The pathophysiology and treatments of airway diseases have been extensively reviewed in the literature (for reference see Barnes, P.J. Chest, 1997, 111:2, pp 17S-26S and Bryan, S.A. et al, Expert Opinion on investigational drugs, 2000, 9:1, pp25-42) and therefore only a brief summary will be included here to provide some background information.

Glucocorticosteroids, anti-leukotrienes, theophylline, cromones, anti-cholinergics and β2 agonists constitute drug classes that are currently used to treat allergic and non-allergic airways diseases such as asthma and chronic obstructive airways disease (COPD). Treatment guidelines for these diseases include both short and long acting inhaled β2 agonists. Short acting, rapid onset β2 agonists are used for "rescue" bronchodilation, whereas, long-acting forms provide sustained relief and are used as maintenance therapy.

Bronchodilation is mediated via agonism of the β2 adrenoceptor expressed on airway smooth muscle cells, which results in relaxation and hence bronchodilation. Thus, as functional antagonists, β2 agonists can prevent and reverse the effects of all bronchoconstrictor substances, including leukotriene D4 (LTD4), acetylcholine, bradykinin, prostaglandins, histamine and endothelins. Because β2 receptors are so widely distributed in the airway, β2 agonists may also affect other types of cells that play a role in asthma. For example, it has been reported that β2 agonists may stabilize mast cells. The inhibition of the release of bronchoconstrictor substances may be how β2 agonists block the bronchoconstriction induced by allergens, exercise and cold air. Furthermore, β2 agonists inhibit cholinergic neurotransmission in the human airway, which can result in reduced cholinergic-reflex bronchoconstriction.

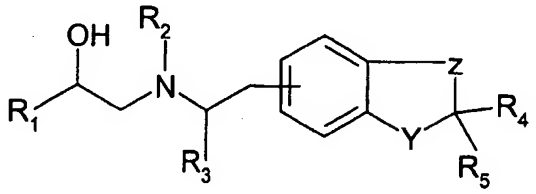
In addition to the airways, it has also been established that β2 adrenoceptors are also expressed in other organs and tissues and thus β2 agonists may have application in the treatment of other diseases such as, but not limited to those of the nervous system, premature labor, congestive heart failure, depression, inflammatory and allergic skin diseases, psoriasis, proliferative skin diseases, glaucoma and in conditions where there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

However, numerous β2 agonists are limited in their use due to their low selectivity or adverse side-effects driven by high systemic exposure and mainly mediated through action at β2 adrenoreceptors expressed outside the airways

(muscle tremor, tachycardia, palpitations, restlessness). Therefore there is a need for improved agents in this class.

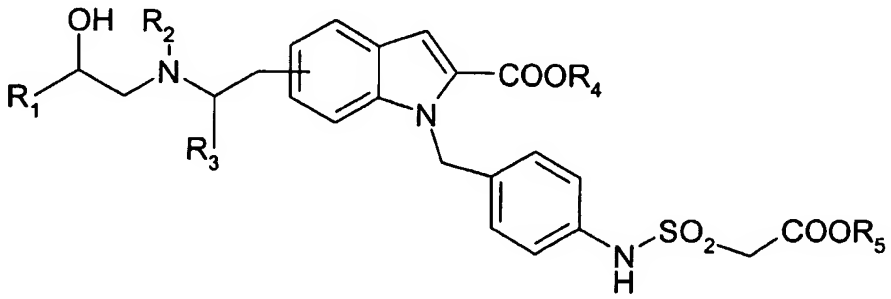
Accordingly, there is still a need for novel β2 agonists that would have an appropriate pharmacological profile, for example in terms of potency. In this context, the present invention relates to novel β2 agonists of the indole derivatives family.

Various indole derivatives have already been synthesised. For example, the patent application EP 801 060 discloses dihydroindole derivatives having a selective β3 agonist activity, of formula :



wherein R_1 may be an optionally substituted phenyl (1 to 3 substitutents which may be selected from hydroxyl and hydroxyalkyl), R_2 may be hydrogen, R_3 is hydrogen or alkyl, Z is $-CH_2-$ or $-CH_2-CH_2-$, Y may be $-NR_7-$ (R_7 may be hydrogen and alkyl) and R_4 and R_5 are independently hydrogen, $COOR_6$, $COONR_6R_6$, CHO, COR_6, CH_2OH, $CH_2OCH_2COOR_6$ and $CH_2OCH_2CH_2OR_6$ (R_6 is hydrogen or alkyl).

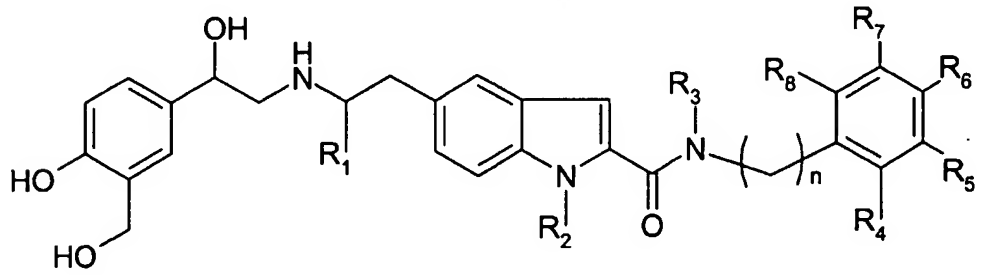
Another example concerns the patent application EP 822 185 that also discloses selective β3 agonists of formula :



wherein R_1 may be an optionally substituted phenyl with 1 to 3 substitutents selected from hydroxy and hydroxyalkyl, R_2 may be hydrogen, and R_3 may be hydrogen or alkyl optionally independently substituted with one or more halo atoms.

However, none of the indole derivatives synthesised so far have shown β2 agonist activity with high potency (they are all selective β3 agonists) allowing them to be used as efficient drugs in the treatment of the β2-mediated diseases and/or conditions, in particular allergic and non-allergic airways diseases.

It has now been found that the new indole derivatives of general formula (1):



(1)

wherein

- n is an integer equal to 0, 1, 2, 3 or 4;
- R_1 and R_2 are each independently selected from hydrogen and (C_1-C_4)alkyl;
- R_3 is selected from the group consisting of hydrogen or (C_1-C_6)alkyl optionally substituted by a hydroxy; and
- R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, benzyloxy, hydroxy(C_1-C_6)alkyl, thio(C_1-C_6)alkyl, halo and trifluoromethyl,

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof,

are agonists of the β2 receptors, that are particularly useful for the treatment of β2-mediated diseases and/or conditions, by showing good potency, in particular when administered via the inhalation route.

In the present invention, the term "potent" means that the compounds of formula (1) show an agonist potency for the β2 receptor, which is less than 10 nM as measured by the cell-based assay described herein.

In the here above general formula (1), (C_1-C_4) radicals denote a straight-chain or branched group containing 1, 2, 3 or 4 carbon atoms and (C_1-C_6)alkyl radicals denote a straight-chain or branched group containing 1, 2, 3, 4, 5 or 6 carbon atoms respectively. This also applies if they carry substituents or occur as substituents of other radicals, for example in (C_1-C_6)alkoxy radicals, hydroxy(C_1-C_6)alkyl radicals, thio(C_1-C_6)alkyl radicals etc... . Examples of suitable (C_1-C_6)alkyl radicals are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *tert*-pentyl, *n*-hexyl, *iso*-hexyl, 3-methylpentyl etc.... Examples of suitable (C_1-C_6)alkoxy radicals are methoxy, ethoxy, *n*-propyloxy, *iso*-propyloxy, *n*-butyloxy, *iso*-butyloxy, *sec*-butyloxy and *tert*-butyloxy, *n*-pentyloxy, *iso*-pentyloxy, *tert*-pentyloxy, *n*-hexyloxy, *iso*-hexyloxy, 3-methylpentyloxy etc.... Hydroxy(C_1-C_6)alkyl radicals are alkyl radicals substituted by a hydroxy group (-OH). According to a preferred embodiment of said invention, such radicals contain one hydroxy substituent. Examples of suitable hydroxy(C_1-C_6)alkyl radicals are hydroxymethyl, 1-hydroxyethyl or 2-hydroxyethyl. Thio(C_1-C_6)alkyl radicals are alkyl radicals attached to through a –S- atom, i.e. thio(C_1-C_6)alkyl means –S-alkyl. Examples of suitable thio(C_1-C_6)alkyl radicals are thiomethyl, thioethyl, thiopropyl etc...

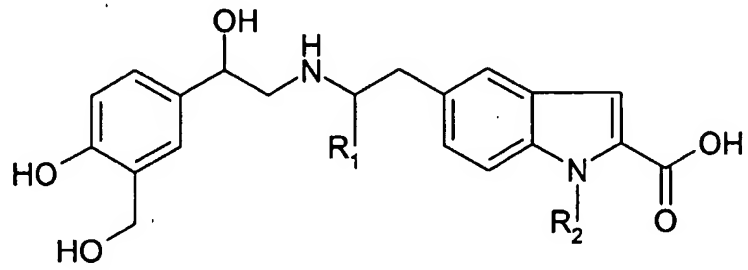
In the general formula (1) according to the present invention, when a radical is mono- or poly-substituted, said substituent(s) can be located at any desired position(s). Also, when a radical is polysubstituted, said substituents can be identical or different.

Finally, halo denotes a halogen atom selected from the group consisting of fluoro, chloro, bromo and iodo in particular fluoro or chloro.

The indole derivatives of the formula (1) can be prepared using conventional procedures such as by the following illustrative methods in which

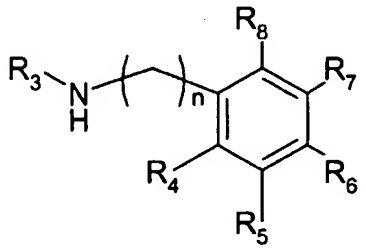
R_1 to R_8 and n are as previously defined for the indole derivatives of the formula (1) unless otherwise stated.

The indole derivatives of the formula (1) may be prepared by coupling an acid of formula (2) :



(2)

with an amine of formula (3) :

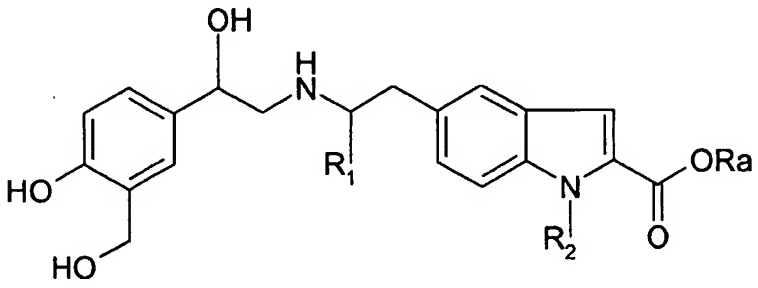


(3)

wherein n and R_1 to R_8 are as previously defined. The coupling is generally carried out in an excess of said amine as an acid receptor, with a conventional coupling agent (e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride or N,N'-dicyclohexylcarbodiimide), optionally in the presence of a catalyst (e.g. 1-hydroxybenzotriazole hydrate or 1-hydroxy-7-azabenzotriazole), and optionally in the presence of a tertiary amine base (e.g. N-methylmorpholine, triethylamine or diisopropylethylamine). The reaction may be undertaken in a suitable solvent such as pyridine, dimethylformamide, tetrahydrofuran, dimethylsulfoxide, dichloromethane or ethyl acetate, and at temperature comprised between 10°C and 40°C (room temperature). It may also be necessary to further manipulate a structure of compound of formula (1) to yield another desired compound of formula (1). For example, to yield a hydroxy substituent from a benzyloxy substituent, a hydrogenation reaction can be performed typically at 15-60 psi in a solvent such as methanol or ethanol at ambient or up to 50 °C.

Said amine (3) is either commercially available or may be prepared by conventional methods well known to the one skilled in the art (e.g. reduction, oxidation, alkylation, protection, deprotection etc...) from commercially available material.

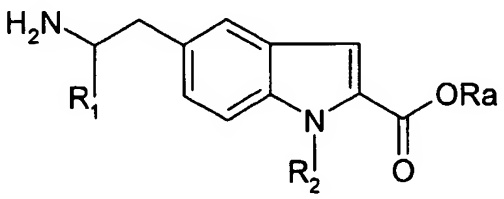
The acid of formula (2) may be prepared from the corresponding ester of formula (4) :



(4)

wherein Ra is a suitable acid protecting group, preferably a (C_1-C_4)alkyl group, which includes, but is not limited to, methyl and ethyl,
according to any method well-known to the one skilled in the art to prepare an acid from an ester, without modifying the rest of the molecule. For example, the ester may be hydrolysed by treatment with aqueous acid or base (e.g. hydrogen chloride, potassium hydroxide, sodium hydroxide or lithium hydroxide), optionally in the presence of a solvent or mixture of solvents (e.g. water, 1,4-dioxan, tetrahydrofuran/water), at a temperature comprised between 20°C and 100°C, for a period of 1 to 40 hours.

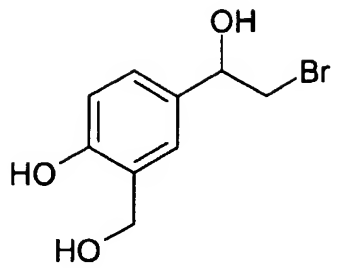
The ester of formula (4) may be prepared by reaction of an amine of formula (5) :



(5)

wherein Ra is as previously defined,

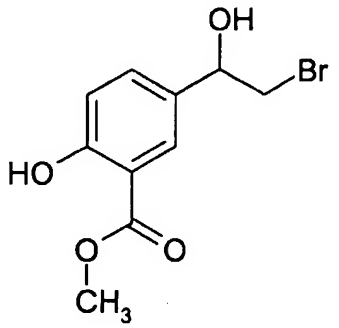
with a bromide of formula (6) :



(6)

In a typical procedure, the amine of formula (5) or a salt thereof is reacted with a bromide of formula (6) optionally in the presence of a solvent or mixture of solvents (e.g. dimethyl sulphoxide, toluene, N,N-dimethylformamide, acetonitrile), optionally in the presence of a suitable base (e.g. triethylamine, diisopropylethylamine, potassium carbonate), optionally in the presence of a catalyst such as NaI at a temperature comprised between 80°C and 120°C, for 12 to 48 hours.

The bromide of formula (6) may be prepared from the ester of formula (7) :



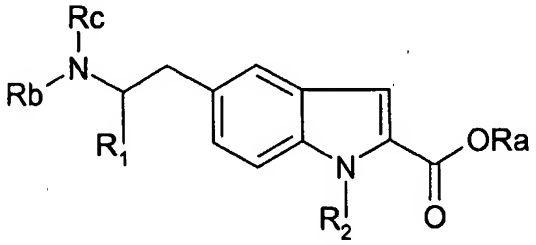
(7)

according to any method well-known to the one skilled in the art to prepare an alcohol from an ester, without modifying the rest of the molecule.

In a typical procedure, the ester of formula (7) is reduced with borane methylsulfide complex in tetrahydrofuran at a reflux for a period of 2 hours or with a BH_3/tetrahydrofuran complex in tetrahydrofuran at a temperature comprised between 40 to 60°C for a period of 5 to 7 hours.

The alcohol of formula (7) may be prepared as either the (*R*) or (*S*) enantiomer according to methods well described in the literature (Tetrahedron Letters 1994, 35(50), 9375).

The amine of formula (5) may be prepared as either the (*R*) or (*S*) enantiomer from the corresponding protected indole of formula (8) :

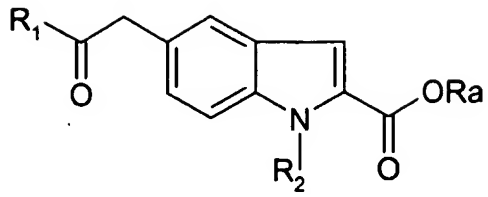


(8)

wherein Ra is as previously defined and Rb and Rc represent any suitable substituents so that HNRbRc is a chiral amine (for example, Rb may be hydrogen and Rc may be a α-methylbenzyl group), provided that the bonds between N and Rb and N and Rc can be easily cleaved to give the free amine of formula (5) or a salt thereof, using standard methodology for cleaving nitrogen protecting groups, such as that found in the text book (see for example T.W. GREENE, Protective Groups in Organic Synthesis , A. Wiley-Interscience Publication, 1981).

In a typical procedure, the amine of formula (8) is reacted with a catalyst such as $Pd(OH)_2/C$ in a solvent such as methanol at a temperature comprised between 60 and 100°C, preferably 80°C for a period of 20 to 40 min, preferably 30 min.

The amine of formula (8) as a single diastereomer may be prepared by reaction of an amine of formula HNRbRc with a ketone of formula (9) :

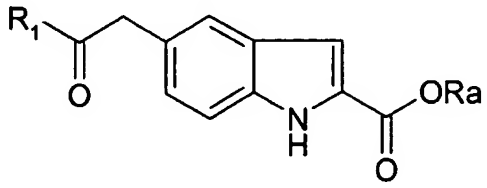


(9)

wherein R_1, R_2, Ra, Rb and Rc are as previously defined.

In a typical procedure, the reaction of the ketone of formula (9) with the amine of formula HNRbRc leads to a chiral intermediate which is in turn reduced by a suitable reducing agent (e.g. sodium cyanoborohydride of formula $NaCNBH_3$ or sodium triacetoxyborohydride of formula $Na(OAc)_3BH$) optionally in the presence of a drying agent (e.g. molecular sieves, magnesium sulfate) and optionally in the presence of an acid catalyst (e.g. acetic acid) to give the amine of formula (8). The reaction is generally done in a solvent such as tetrahydrofuran, toluene or dichloromethane at a temperature comprised between 20°C and 80°C for 3 to 72 hours. The product is then converted to the hydrochloride salt and selectively crystallised from a suitable solvent or mixture of solvents (e.g. isopropanol, ethanol, methanol, diisopropyl ether or diisopropyl ether/methanol) to give the chiral product of formula (8) or its enantiomer if the opposite enantiomer of the amine NHRbRc is used.

The ketone of formula (9) may be prepared by alkylation of a compound of formula (10) :



(10)

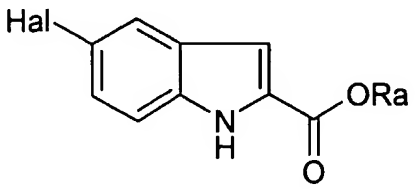
wherein R_1 and Ra are as previously defined.

In a typical procedure, the compound of formula (10) may be alkylated with a suitable alkylating agent (e.g. R_2Br or R_2I) in the presence of a suitable base (e.g. sodium hydride). The reaction is generally done in a solvent such as

tetrahydrofuran or dimethylformamide, at a temperature comprised between -10°C and 80°C for 1 to 16 hours.

It will be appreciated by the person skilled in the art that the introduction of NHRbRc may occur prior to the introduction of R_2.

The ketone of formula (10) may be prepared by palladium mediated coupling of an aryl halide of formula (11) :

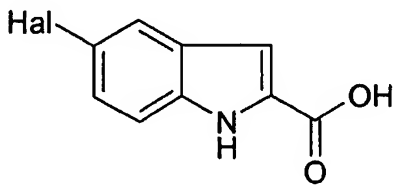


(11)

wherein Ra is as previously defined and Hal represents an halogen atom, which includes, but is not limited to bromo and iodo,
with an enolate or enolate equivalent.

In a typical procedure, the aryl halide of formula (11) is reacted with a tin enolate generated in-situ by treatment of isoprenyl acetate with tri-n-butyltin methoxide of formula Bu_3SnOMe in the presence of a suitable palladium catalyst (palladium acetate/ tri-ortho-tolylphosphine of formula $Pd(OAc)_2/P(o\text{-}Tol)_3$) in a non-polar solvent (e.g. toluene, benzene, hexane). Preferably, the reaction is carried out at a temperature comprised between 80°C and 110°C for 6 to 16 hours.

The aryl halide of formula (11) may be obtained by esterification of the corresponding acid of formula (12) :



(12)

wherein Hal is as previously defined,

according to any method well-known to the one skilled in the art to prepare an ester from an acid, without modifying the rest of the molecule.

In a typical procedure, the acid of formula (12) is reacted with an alcoholic solvent of formula RaOH, wherein Ra is as previously defined, in the presence of an acid such as hydrogen chloride at a temperature between 10°C and 40°C (room temperature) for 8 to 16 hours.

In another typical procedure, the acid of formula (12) is reacted with an alcoholic solvent of formula RaOH, wherein Ra is as previously defined, in the presence of an acyl halide such as acetyl chloride at a temperature between 5°C to 80°C for a perid of 4 to 10 hours.

The acid of formula (12) is a commercial product.

All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the examples and preparations hereto.

For some of the steps of the here above described process of preparation of the indole derivatives of formula (1), it can be necessary to protect the potential reactive functions that are not wished to react, and to cleave said protecting groups in consequence. In such a case, any compatible protecting radical can be used. In particular methods of protection and deprotection such as those described by T.W. GREENE (*Protective Groups in Organic Synthesis*, A. Wiley-Interscience Publication, 1981) or by P. J. Kocienski (*Protecting groups*, Georg Thieme Verlag, 1994), can be used.

For example, when R^2 is hydrogen, the compound of formula (11) may be reacted with a protecting group such as di-tert-butyldicarbonate, in the presence of a base such as N,N-dimethylaminopyridin and of , in a sovent such as toluene. This protecting group may then be removed at the stage of

compound of formula (9) by reacting compound of formula (8) with an acylchloride such as acetyl chloride in the presence of a solvent or a mixture of solvents such as methanol and toluene.

Also, the indole derivatives of formula (1) as well as intermediate for the preparation thereof can be purified according to various well-known methods, such as for example crystallization or chromatography.

Preferred compounds of formula (1) are those wherein

- n is 1 or 2;
- R_1 is a $(C_1$-$C_4)$alkyl;
- R_2 is selected from hydrogen and $(C_1$-$C_4)$alkyl;
- R_3 is selected from hydrogen and $(C_1$-$C_6)$alkyl; and,
- R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, benzyloxy, hydroxy$(C_1$-$C_6)$alkyl, thio$(C_1$-$C_6)$alkyl, halo and trifluoromethyl,

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof.

More preferred compounds of formula (1) are those wherein

- n is an integer equal to 1 or 2;
- R_1 is selected from methyl and ethyl
- R_2 is selected from hydrogen, methyl and ethyl;
- R_3 is selected from hydrogen and methyl; and
- R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, benzyloxy, hydroxy$(C_1$-$C_6)$alkyl, thio$(C_1$-$C_6)$alkyl, halo and trifluoromethyl,

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof,

Still more preferred compounds are those wherein

- n is an integer equal to 1 or 2;
- R_1 is selected from methyl and ethyl;
- R_2 is selected from hydrogen, methyl and ethyl;
- R_3 is selected from hydrogen or methyl; and
- R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, hydroxy, methyl, methoxy, ethoxy, benzyloxy, thiomethyl, halo and trifluoromethyl,

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof,

Preferably, at least 2 of R_4, R_5, R_6, R_7 and R_8 are hydrogen.

Particularly preferred are the indole derivatives of the formula (1) in which n is equal to 1 or 2, R_1 is methyl, R_2 and R_3 are hydrogen atoms, and R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxy$(C_1$-$C_6)$alkyl, thio$(C_1$-$C_6)$alkyl, halo and trifluoromethyl,
or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof.

More particularly preferred are the indole derivatives of the formula (1) in which n is equal to 1, R_1 is methyl, R_2 and R_3 are hydrogen atoms, and R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, thio$(C_1$-$C_6)$alkyl and trifluoromethyl
or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof.

Still more particularly preferred are the indole derivatives of the formula (1) in which n is equal to 1, R_1 is methyl, R_2 and R_3 are hydrogen atoms, and R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of

hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy and trifluoromethyl, provided that at least 2 of R_4, R_5, R_6, R_7 and R_8 are hydrogen,
or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof.

Still more particularly preferred are the indole derivatives of the formula (1) in which n is equal to 1, R_1 is methyl, R_2 and R_3 are hydrogen atoms, and R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, methyl, methoxy and trifluoromethyl provided that at least 2 of R_4, R_5, R_6, R_7 and R_8 are hydrogen,
or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates or isotopic variations thereof.

Particularly preferred are the indole derivatives of the formula (1) as described in the Examples section hereafter, i.e. :

5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino) propyl]-*N*-(2-methoxybenzyl)-1*H*-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl} amino) propyl]-*N*-[4-(trifluoromethyl)benzyl]-1*H*-indole-2-carboxamide,

N-(2,6-dimethoxybenzyl)-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxy-methyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino) propyl]-*N*-(3-methoxybenzyl)-1*H*-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino) propyl]-*N*-[2-(3-methoxyphenyl)ethyl]-1*H*-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(2,4-dichlorobenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(3-hydroxy-2,6-dimethoxybenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-benzyloxy-3-hydroxy methyl phenyl)ethyl} amino)propyl}-*N*-(2-benzyloxy-6-methoxybenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(4-hydroxy-2,6-dimethoxybenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-benzyloxy-6-methoxybenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-hydroxy-6-methoxybenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2,6-difluorobenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-chlorobenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-fluorobenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(4-hydroxybenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(3-hydroxybenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-methylsulfanylbenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(4-methylsulfanylbenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2,3-dimethoxybenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2,4-dimethoxybenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-ethoxybenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-benzyl-*N*-methyl-1H-indole-2-carboxamide,

[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-benzyl-1H-indole-2-carboxamide,

[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(4-fluorobenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-methoxy-3-methyl-benzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(3-methoxy-2-methylbenzyl)-1H-indole-2-carboxamide,

1-Ethyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl} amino)propyl}-*N*-(2,6-dimethoxybenzyl)-1H-indole-2-carboxamide,

1-Ethyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl} amino)propyl}-*N*-(2-ethoxybenzyl)-1H-indole-2-carboxamide,

1-Ethyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl} amino)propyl}-*N*-(4-chlorobenzyl)-1H-indole-2-carboxamide,

1-Methyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl} amino)propyl}-*N*-(2,6-dimethoxybenzyl)-1H-indole-2-carboxamide,

1-Methyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl} amino)propyl}-*N*-(2-methoxybenzyl)-1H-indole-2-carboxamide,

1-Methyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl} amino)propyl}-*N*-(4-chlorobenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) butyl}-*N*-(2-methoxybenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) butyl}-*N*-(2,6-dimethoxybenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) butyl}-*N*-(2-ethoxybenzyl)-1H-indole-2-carboxamide, and,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) butyl}-*N*-benzyl-1H-indole-2-carboxamide.

More preferred compounds according to the invention are:

5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino)propyl]-*N*-(2-methoxybenzyl)-1*H*-indole-2-carboxamide,

N-(2,6-dimethoxybenzyl)-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino)propyl]-*N*-(3-methoxybenzyl)-1*H*-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino)propyl]-*N*-[2-(3-methoxyphenyl)ethyl]-1*H*-indole-2-carboxamide, and,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(3-hydroxy-2,6-dimethoxybenzyl)-1H-indole-2-carboxamide.

The indole derivatives of formula (1) may also be optionally transformed into pharmaceutically acceptable salts. In particular, these pharmaceutically

acceptable salts of the indole derivatives of the formula (1) include the acid addition and the base salts (including disalts) thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate, camsylate, citrate, edisylate, esylate, fumarate, gluceptate, gluconate, glucuronate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, hydrogen phosphate, hydrogen sulfate, isethionate, D- and L-lactate, malate, maleate, malonate, mesylate, methylsulphate, 2-napsylate, nicotinate, nitrate, orotate, palmoate, phosphate, saccharate, stearate, succinate sulphate, D- and L-tartrate, 1-hydroxy-2-naphthoate and tosylate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Compounds which contain both acidic groups and basic groups can also be present in the form of internal salts or betaines, which are also included by the present invention. For a review on suitable salts, see Stahl and Wermuth, Handbook of Pharmaceutical Salts: Properties, Selection, and Use, Wiley-VCH, Weinheim, Germany (2002).

Salts can generally be obtained from the indole derivatives of the formula (1) according to customary procedures known to the person skilled in the art, for example by combining with an organic or inorganic acid or base in a suitable solvent or dispersant, or alternatively from other salts by anion exchange or cation exchange. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

Pharmaceutically acceptable solvates in accordance with the invention include hydrates and solvates wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Also within the scope of the invention are clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in non-stoichiometric amounts. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

Also within the scope of the invention are so-called "prodrugs" of the compounds of formula (1). Thus certain derivatives of compounds of formula (1) which have little or no pharmacological activity themselves can, when metabolised upon administration into or onto the body, give rise to compounds of formula (1) having the desired activity. Such derivatives are referred to as "prodrugs".

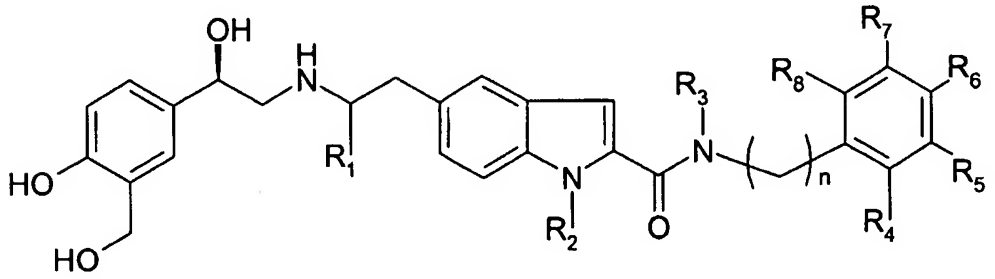
Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (1) with certain moieties known to those skilled in the art as "pro-moieties" as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

Finally, certain compounds of formula (1) may themselves act as prodrugs of other compounds of formula (1).

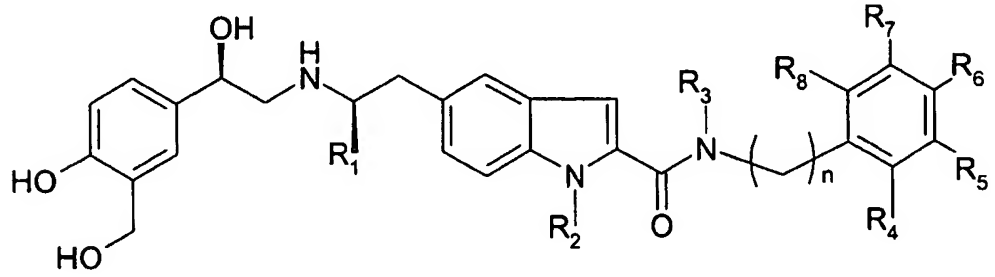
The indole derivatives of the formula (1) can also be present in stereoisomeric forms. If the indole derivatives of the formula (1) contain one or more centres of asymmetry, these can independently of one another have the (S) configuration or the (R) configuration. The invention includes all possible stereoisomers of the indole derivatives of the formula (1), for example enantiomers and diastereomers, and mixtures of two or more stereoisomeric forms, for example mixtures of enantiomers and/or diastereomers, in all ratios. The invention thus relates to enantiomers in enantiomerically pure form, both as levorotatory and dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. The invention likewise relates to diastereomers in diastereomerically pure form and in the form of

mixtures in all ratios. In the presence of cis/trans isomerism, the invention relates to both the cis form and the trans form and mixtures of these forms in all ratios. Individual stereoisomers can be prepared, if desired, by use of stereochemically homogeneous starting substances in the synthesis, by stereoselective synthesis or by separation of a mixture according to customary methods, for example by chromatography, crystallization or by chromatography on chiral phases. If appropriate, derivatization can be carried out before separation of stereoisomers. A stereoisomer mixture can be separated at the stage of the indole derivatives of the formula (1) or at the stage of a starting substance or of an intermediate in the course of the synthesis.

According to one aspect of the present invention, the following R-stereoisomer wherein R_1 to R_8 and n are as defined above, is generally preferred,



When R_1 is (C_1-C_4)alkyl, the following (R,R)-stereoisomer wherein R_1 to R_8 and n are as defined above, is generally preferred,



The compounds of the formula (1) according to the invention can moreover contain mobile hydrogen atoms, i.e. be present in various tautomeric

forms. The present invention also relates to all tautomers of the compounds of the formula (1).

The present invention furthermore includes other types of derivatives of indole derivatives of the formula (1), for example, solvates such as hydrates and polymorphs, i.e. the various different crystalline structures of the indole derivatives according to the present invention.

The present invention also includes all suitable isotopic variations of the indole derivatives of the formula (1) or a pharmaceutically acceptable salt thereof. An isotopic variation of the indole derivatives of the formula (1) or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into the indole derivatives of the formula (1) and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, sulphur, fluorine and chlorine such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{35}S, ^{18}F and ^{36}Cl, respectively. Certain isotopic variations of the indole derivatives of the formula (1) and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the indole derivatives of the formula (1) and pharmaceutically acceptable salts thereof of this invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples and Preparations sections hereafter using appropriate isotopic variations of suitable reagents.

According to a further aspect, the present invention concerns mixtures of indole derivatives of the formula (1), as well as mixtures with or of their pharmaceutically acceptable salts, solvates, isomeric forms and/or isotope forms.

According to the present invention, all the here above mentioned forms of the indole derivatives of formula (1) except the pharmaceutically acceptable salts (i.e. said solvates, isomeric forms, tautomers, clathrate and isotope forms), are defined as "derived forms" of the indole derivatives of formula (1) in what follows (including the claims).

The indole derivatives of formula (1), their pharmaceutically acceptable salts and/or derived forms, are valuable pharmaceutically active compounds, which are suitable for the therapy and prophylaxis of numerous disorders in which the β2 receptor is involved or in which agonism of this receptor may induce benefit, in particular the allergic and non-allergic airways diseases.

The indole derivatives of formula (1) and their pharmaceutically acceptable salts and derived forms as mentioned above can be administered according to the invention to animals, preferably to mammals, and in particular to humans, as pharmaceuticals for therapy and/or prophylaxis. They can be administered per se, in mixtures with one another or in the form of pharmaceutical preparations which as active constituent contain an efficacious dose of at least one indole derivative of the formula (1), its pharmaceutically acceptable salts and/or derived forms, in addition to customary pharmaceutically innocuous excipients and/or additives.

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms may be freeze-dried, spray-dried, or evaporatively dried to provide a solid plug, powder, or film of crystalline or amorphous material. Microwave or radio frequency drying may be used for this purpose.

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms may be administered alone or in combination with other

drugs and will generally be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound of the invention. The choice of excipient will to a large extent depend on the particular mode of administration.

In the present case, the inhalation route is preferred.

ORAL ADMINISTRATION

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

The composition of a typical tablet in accordance with the invention may comprise:

Ingredient	% w/w
Compound of formula (1)	10.00*
Microcrystalline cellulose	64.12
Lactose	21.38
Croscarmellose sodium	3.00
Magnesium stearate	1.50

* Quantity adjusted in accordance with drug activity.

A typical tablet may be prepared using standard processes known to a formulation chemist, for example, by direct compression, granulation (dry, wet, or melt), melt congealing, or extrusion. The tablet formulation may comprise one or more layers and may be coated or uncoated.

Examples of excipients suitable for oral administration include carriers, for example, cellulose, calcium carbonate, dibasic calcium phosphate, mannitol and sodium citrate, granulation binders, for example, polyvinylpyrrolidine, hydroxypropylcellulose, hydroxypropylmethylcellulose and gelatin, disintegrants, for example, sodium starch glycolate and silicates, lubricating agents, for example, magnesium stearate and stearic acid, wetting agents, for example, sodium lauryl sulphate, preservatives, anti-oxidants, flavours and colourants.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release. Details of suitable modified release technologies such as high energy dispersions, osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical

Technology On-line, 25(2), 1-14 (2001). Other modified release formulations are described in US Patent No. 6,106,864.

PARENTERAL ADMINISTRATION

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms used in the preparation of parenteral solutions may be increased by suitable processing, for example, the use of high energy spray-dried dispersions (see WO 01/47495) and/or by the use of appropriate formulation techniques, such as the use of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release.

TOPICAL ADMINISTRATION

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms may also be administered topically to the skin or mucosa, either dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by iontophoresis, electroporation, phonophoresis, sonophoresis and needle-free or microneedle injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release. Thus compounds of the invention may be formulated in a more solid form for administration as an implanted depot providing long-term release of the active compound.

INHALED/INTRANASAL ADMINISTRATION

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose in anhydrous or monohydrate form, preferably monohydate, mannitol, dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose or trehalose, or as a mixed component particle, for example, mixed with

phospholipids) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as dichlorofluoromethane.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the active compound comprising, for example, ethanol (optionally, aqueous ethanol) or a suitable alternative agent for dispersing, solubilising, or extending release of the active, the propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1μg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1μl to 100μl. A typical formulation may comprise a compound of formula (1), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Capsules, blisters and cartridges (made, for example, from gelatin or HPMC) for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose,or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 0.001mg to 10mg of the compound of formula (1). The overall daily dose will typically be in the range 0.001mg to 40mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled, dual-, targeted and programmed release.

Flavouring agent such as menthol or levomenthol and/or sweeteners such as saccharin or saccharin sodium can be added to the formulation

RECTAL/INTRAVAGINAL ADMINISTRATION

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release.

OCULAR/ANDIAL ADMINISTRATION

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms may also be administered directly to the eye or ear, typically in

the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and andial administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/andial administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted, or programmed release.

ENABLING TECHNOLOGIES

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms may be combined with soluble macromolecular entities such as cyclodextrin or polyethylene glycol-containing polymers to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

DOSAGE

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 0.001mg to 5000mg depending, of course, on the mode of administration. For example, oral administration may require a total daily dose of from 1mg to 5000mg, while an inhaled dose may only require from 0.001mg to 40mg. The total daily dose may be administered in single or divided doses.

These dosages are based on an average human subject having a weight of about 65 to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

According to another embodiment of the present invention, the indole derivatives of the formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, can also be used as a combination with one or more additional therapeutic agents to be co-administered to a patient to obtain some particularly desired therapeutic end result such as the treatment of pathophysiologically-relevant disease processes including, but not limited to (i) bronchoconstriction, (ii) inflammation, (iii) allergy, (iv) tissue destruction, (v) signs and symptoms such as breathlessness, cough. The second and more additional therapeutic agents may also be an indole derivative of the formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, or one or more β2 agonists known in the art. More typically, the second and more therapeutic agents will be selected from a different class of therapeutic agents.

As used herein, the terms "co-administration", "co-administered" and "in combination with", referring to the indole derivatives of formula (1) and one or more other therapeutic agents, is intended to mean, and does refer to and include the following :

- simultaneous administration of such combination of indole derivative(s) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components at substantially the same time to said patient,

- substantially simultaneous administration of such combination of indole derivative(s) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at substantially the same time by said patient, whereupon said components are released at substantially the same time to said patient,

- sequential administration of such combination of indole derivative(s) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at consecutive times by said patient with a significant time interval between each administration, whereupon said components are released at substantially different times to said patient; and

- sequential administration of such combination of indole derivative(s) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components in a controlled manner whereupon they are concurrently, consecutively, and/or overlapingly administered at the same and/or different times by said patient,

where each part may be administered by either the same or different route.

Suitable examples of other therapeutic agents which may be used in combination with the indole derivatives of the formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, include, but are by no means limited to :

(a) 5-Lipoxygenase (5-LO) inhibitors or 5-lipoxygenase activating protein (FLAP) antagonists,

(b) Leukotriene antagonists (LTRAs) including antagonists of LTB_4, LTC_4, LTD_4, and LTE_4,

(c) Histamine receptor antagonists including H1 and H3 antagonists,

(d) α_1- and α_2-adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use,

(e) muscarinic M3 receptor antagonists or anticholinergic agents,

(f) PDE inhibitors, e.g. PDE3, PDE4 and PDE5 inhibitors,

(g) Theophylline,

(h) Sodium cromoglycate,

(i) COX inhibitors both non-selective and selective COX-1 or COX-2 inhibitors (NSAIDs),

(j) Oral and inhaled glucocorticosteroids,

(k) Monoclonal antibodies active against endogenous inflammatory entities,

(l) Anti-tumor necrosis factor (anti-TNF-α) agents,

(m)Adhesion molecule inhibitors including VLA-4 antagonists,

(n) Kinin-B_1 - and B_2 -receptor antagonists,

(o) Immunosuppressive agents,

(p) Inhibitors of matrix metalloproteases (MMPs),

(q) Tachykinin NK_1, NK_2 and NK_3 receptor antagonists,

(r) Elastase inhibitors,

(s) Adenosine A2a receptor agonists,

(t) Inhibitors of urokinase,

(u) Compounds that act on dopamine receptors, e.g. D2 agonists,

(v) Modulators of the NF$\kappa\beta$ pathway, e.g. IKK inhibitors,

(w) Agents that can be classed as mucolytics or anti-tussive, and

(x) Antibiotics.

According to the present invention, combination of the indole derivatives of formula (1) with :

- glucocorticosteroids, in particular inhaled glucocorticosteroids with reduced systemic side effects, including prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, ciclesonide, fluticasone propionate, and mometasone furoate, or

- muscarinic M3 receptor antagonists or anticholinergic agents including in particular ipratropium salts, namely bromide, tiotropium salts, namely bromide, oxitropium salts, namely bromide, perenzepine, and telenzepine,

are preferred.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment. The description, which follows, concerns the therapeutic applications to which the indole derivatives of formula (1) may be put.

The indole derivatives of formula (1) have the ability to interact with the β2 receptor and thereby have a wide range of therapeutic applications, as described further below, because of the essential role which the β2 receptor plays in the physiology of all mammals.

Therefore, a further aspect of the present invention relates to the indole derivatives of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for use in the treatment of diseases, disorders, and conditions in which the β2 receptor is involved. More specifically, the present invention also concerns the indole derivatives of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for use in the treatment of diseases, disorders, and conditions selected from the group consisting of :

- asthma of whatever type, etiology, or pathogenesis, in particular asthma that is a member selected from the group consisting of atopic asthma, non-atopic asthma, allergic asthma, atopic bronchial IgE-mediated

asthma, bronchial asthma, essential asthma, true asthma, intrinsic asthma caused by pathophysiologic disturbances, extrinsic asthma caused by environmental factors, essential asthma of unknown or inapparent cause, non-atopic asthma, bronchitic asthma, emphysematous asthma, exercise-induced asthma, allergen induced asthma, cold air induced asthma, occupational asthma, infective asthma caused by bacterial, fungal, protozoal, or viral infection, non-allergic asthma, incipient asthma, wheezy infant syndrome and bronchiolytis,

- chronic or acute bronchoconstriction, chronic bronchitis, small airways obstruction, and emphysema,

- obstructive or inflammatory airways diseases of whatever type, etiology, or pathogenesis, in particular an obstructive or inflammatory airways disease that is a member selected from the group consisting of chronic eosinophilic pneumonia, chronic obstructive pulmonary disease (COPD), COPD that includes chronic bronchitis, pulmonary emphysema or dyspnea associated or not associated with COPD, COPD that is characterized by irreversible, progressive airways obstruction, adult respiratory distress syndrome (ARDS), exacerbation of airways hyper-reactivity consequent to other drug therapy and airways disease that is associated with pulmonary hypertension,

- bronchitis of whatever type, etiology, or pathogenesis, in particular bronchitis that is a member selected from the group consisting of acute bronchitis, acute laryngotracheal bronchitis, arachidic bronchitis, catarrhal bronchitis, croupus bronchitis, dry bronchitis, infectious asthmatic bronchitis, productive bronchitis, staphylococcus or streptococcal bronchitis and vesicular bronchitis,

- bronchiectasis of whatever type, etiology, or pathogenesis, in particular bronchiectasis that is a member selected from the group consisting of cylindric bronchiectasis, sacculated bronchiectasis, fusiform

bronchiectasis, capillary bronchiectasis, cystic bronchiectasis, dry bronchiectasis and follicular bronchiectasis,

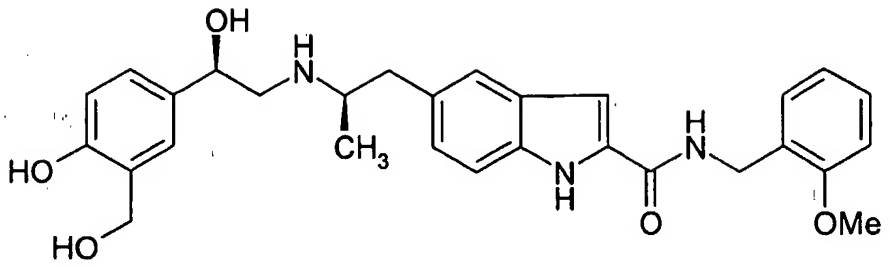
- premature labor, and other type of diseases and conditions such as inflammatory and allergic skin diseases, psoriasis and proliferative skin diseases.

A still further aspect of the present invention also relates to the use of the indole derivatives of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for the manufacture of a drug having a β2 agonist activity. In particular, the present inventions concerns the use of the indole derivatives of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for the manufacture of a drug for the treatment of β2-mediated diseases and/or conditions, in particular the diseases and/or conditions listed above.

As a consequence, the present invention provides a particularly interesting method of treatment of a mammal, including a human being, including treating said mammal with an effective amount of an indole derivative of formula (1), or a pharmaceutically acceptable salt, derived form or composition thereof. More precisely, the present invention provides a particularly interesting method of treatment of a mammal, including a human being, to treat a β2-mediated diseases and/or conditions, in particular the diseases and/or conditions listed above, including treating said mammal with an effective amount of an indole derivative of formula (1), its pharmaceutically acceptable salts and/or derived forms.

The following examples illustrate the preparation of the indole derivatives of the formula (1) :

EXAMPLE 1 : 5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino)propyl]-*N*-(2-methoxybenzyl)-1*H*-indole-2-carboxamide



A solution of 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(2-methoxybenzyl)-1*H*-indole-2-carboxamide (Preparation 1, 67 mg, 0.11 mmol) in a mixture of methanol (4.0 ml) and water (2.4 ml) was treated with ammonium fluoride (40 mg, 1.08 mmol) and the resulting suspension heated at 40°C for a period of 16 hours. The solvent was removed in vacuo and the residue purified by flash column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (95:5:0.5 changing to 85:15:1.5, by volume) to give the title compound as a colourless solid (38 mg).

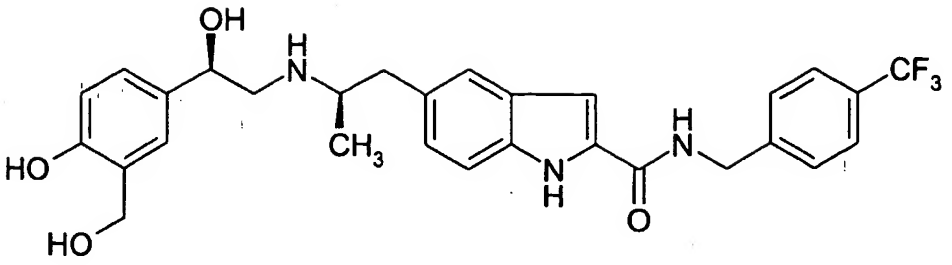
^{1}H NMR (400 MHz, CD_3OD) : δ = 7.35-7.19 (5H, m), 7.03-6.96 (4H, m), 6.93-6.89 (1H, m), 6.63-6.61 (1H, d), 4.65-4.62 (1H, m), 4.59 (2H, s), 4.57 (2H, s), 3.88 (3H, s), 3.09-3.04 (1H, m), 2.98-2.93 (1H, m), 2.85-2.69 (3H, m), 1.14-1.12 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 504.

Analysis : Found C 65.86; H 6.57; N 7.71; $C_{29}H_{33}N_3O_5$. $1.4H_2O$ requires C 65.87; H 6.82; N 7.95.

Optical Rotation $[\alpha]^D_{25}$ = -351.07° 0.4mg/ml MeOH, 365nm

EXAMPLE 2 : 5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-[4-(trifluoromethyl)benzyl]-1*H*-indole-2-carboxamide

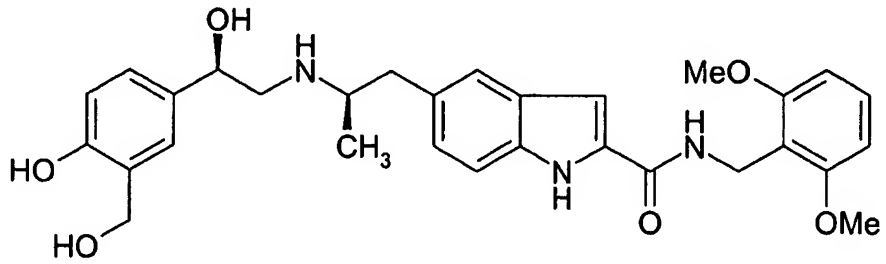


Prepared from 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-[4-(trifluoromethyl)benzyl]-1*H*-indole-2-carboxamide (Preparation 2) according to the method described above to give the title compound as a pale yellow foam.

^{1}H NMR (400MHz, CD_3OD): δ = 7.65-7.63 (2H, m), 7.57-7.55 (2H, m), 7.34-7.32 (2H, m), 7.17 (1H, s), 7.03-6.94 (3H, m), 6.60-6.58 (1H, d), 4.67 (2H, s), 4.61-4.58 (1H, m), 4.55 (2H, s), 3.00-2.89 (2H, m), 2.78-2.67 (3H, m), 1.12-1.10 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 542.

EXAMPLE 3 : *N*-(2,6-dimethoxybenzyl)-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxamide



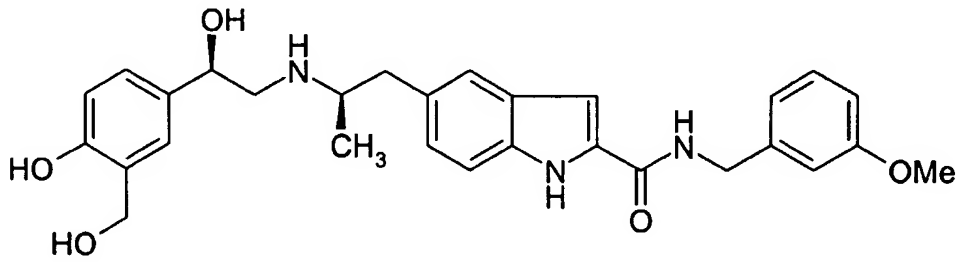
Prepared from 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(2,6-dimethoxybenzyl)-1*H*-indole-2-carboxamide (Preparation 3) according to the method described above to give the title compound as a colourless solid.

^{1}H NMR (400MHz, CD_3OD): δ = 7.29-7.24 (3H, m), 7.16 (1H, bs), 6.97-6.92 (3H, m), 6.66 (2H, d), 6.58 (1H, d), 4.66 (2H, s), 4.59-4.55 (1H, m), 4.54 (2H, s), 3.66 (6H, s), 2.94-2.86 (2H, m), 2.70-2.64 (3H, m), 1.08 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 534, $[M+Na]^+$ 556.

Analysis : Found C 66.42; H 6.69; N 7.88; $C_{29}H_{33}N_3O_5$. $0.52H_2O$ requires C 66.36; H 6.69; N 7.74.

EXAMPLE 4 : 5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino)propyl]-*N*-(3-methoxybenzyl)-1*H*-indole-2-carboxamide

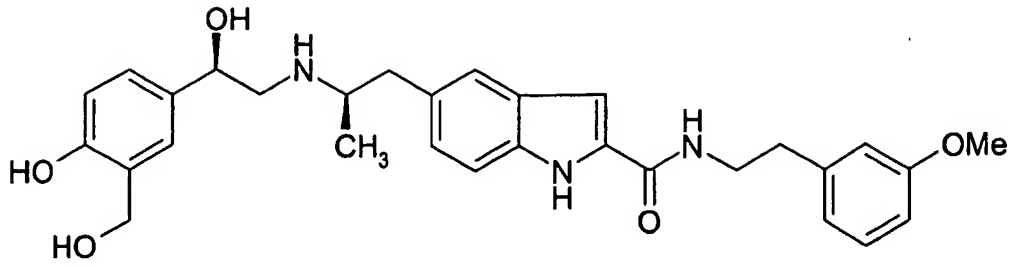


Prepared from 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(3-methoxybenzyl)-1*H*-indole-2-carboxamide (Preparation 4) according to the method described above to give the title compound as a colourless foam.

^{1}H NMR (400MHz, CD_3OD): δ = 7.34-4.31 (2H, d), 7.26-7.21 (1H, t), 7.18-7.17 (1H, m), 7.05-6.94 (5H, m), 6.82-6.80 (1H, m), 6.61-6.59 (1H, d), 4.62-4.56 (5H, m), 3.77 (3H, s), 3.02-2.89 (2H, m), 2.76-2.69 (3H, m), 1.12-1.10 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 504.

EXAMPLE 5 : 5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino)propyl]-*N*-[2-(3-methoxyphenyl)ethyl]-1*H*-indole-2-carboxamide

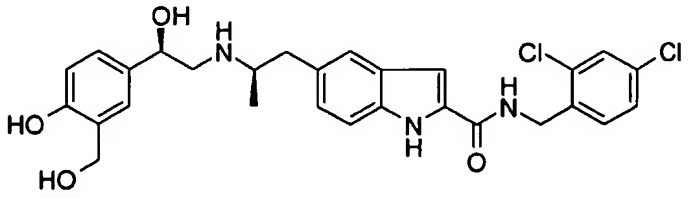


Prepared from 5-[(2R)-2-({(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-N-[2-(3-methoxyphenyl)ethyl]-1H-indole-2-carboxamide (Preparation 5) according to the method described above to give the title compound as a colourless foam.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.33-7.31 (2H, d), 7.21-7.17 (2H, m), 7.01-6.93 (3H, m), 6.85-6.84 (2H, m), 6.77-6.74 (1H, m), 6.61-6.59 (1H, d), 4.63-4.60 (1H, m), 4.56 (2H, s), 3.74 (3H, s), 3.62-3.58 (2H, t), 3.03-2.98 (1H, m), 2.94-2.88 (3H, m), 2.81-2.67 (3H, m), 1.12-1.10 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 518.

Example 6 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl]-*N*-(2,4-dichlorobenzyl)-1H-indole-2-carboxamide

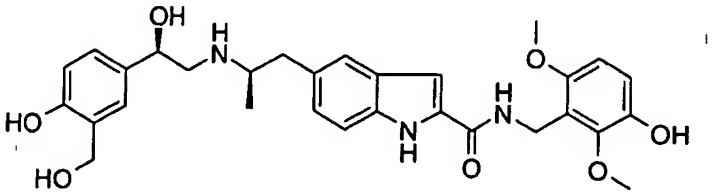


Prepared using the amide from Preparation **6** and the method described for Example **1**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.48-7.47 (1H, d), 7.44-7.42 (1H, d), 7.34-7.30 (3H, m), 7.17 (1H, s), 7.05 (1H, s), 7.03-6.95 (2H, m), 6.61-6.59 (1H, d), 4.65 (2H, s), 4.63-4.59 (1H, m), 4.55 (2H, s), 3.03-2.98 (1H, m), 2.96-2.91 (1H, m), 2.80-2.68 (3H, m), 1.13-1.11 (3H, d) ppm.

LRMS (APCI) : m/z $[MH]^+$ 542.

Example 7 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl]-*N*-(3-hydroxy-2,6-dimethoxybenzyl)-1H-indole-2-carboxamide

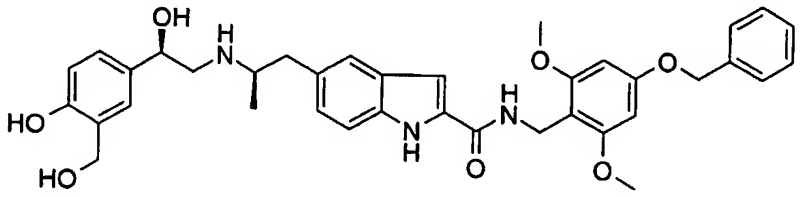


Prepared using the amide from Preparation **8** and the method described for Example **1**.

^{1}H NMR (400MHz, CD_3OD) : δ = 7.30 (2H, m), 7.17 (1H, bd), 6.96 (2H, m), 6.80 (1H, d), 6.64 (1H, d), 6.60 (1H, d), 4.65 (3H, s), 4.60 (1H, m), 4.55 (2H, s), 3.85 (3H, s), 3.81 (3H, s), 2.95 (2H, m), 2.72 (3H, m), 1.10 (3H, d) ppm.

LRMS (ESI) : m/z $[M+Na]^+$ 572.

Example 8 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-benzyloxy-3-hydroxy methyl phenyl)ethyl}amino)propyl]-*N*-(2-benzyloxy-6-methoxybenzyl)-1H-indole-2-carboxamide

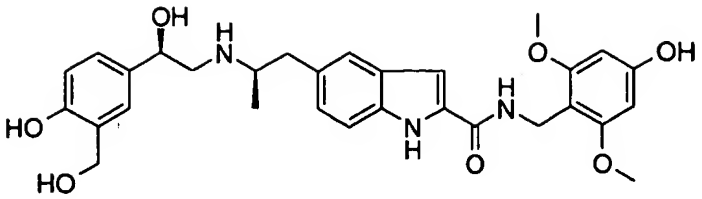


Prepared using the amide from Preparation **9** and the method described for Example **1**.

^{1}H NMR (400MHz, CD_3OD) : δ = 7.45 (2H, m), 7.37 (2H, m), 7.30 (3H, m), 7.16 (1H, d), 6.95 (3H, m), 6.58 (1H, d), 6.32 (2H, s), 5.12 (2H, s), 4.58 (1H, m), 4.56 (2H, s), 4.51 (2H, s), 3.82 (6H, s), 2.90 (2H, m), 2.68 (3H, m), 1.08 (3H, d) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 640, $[M+Na]^+$ 662.

Example 9 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl]-*N*-(4-hydroxy-2,6-dimethoxybenzyl)-1H-indole-2-carboxamide

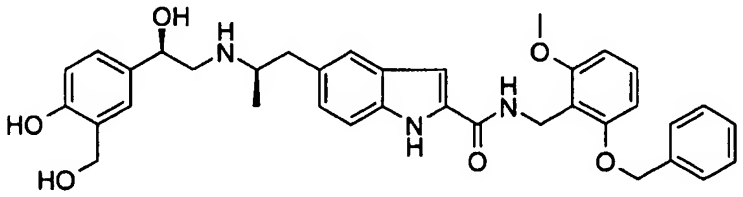


Example **8** (137 mg, 182 μmol) was hydrogenated at 50 psi at 30 °C for 6 h in ethanol (20 ml) in the presence of 10 % palladium–on-carbon catalyst (20 mg). The mixture was filtered through a filter-aid and the solvent removed. The crude material was purified by chromatography (0-7 % MeOH in CH_2Cl_2 and 1 % NH_3) to yield a clear glass (73 mg).

^{1}H NMR (400MHz, CD_3OD) : δ = 7.37 (1H, s), 7.34 (1H, d), 7.24 (1H, bd), 7.03 (2H, bd), 6.96 (1H, s), 6.67 (1H, d), 6.13 (2H, s), 4.71 (1H, m), 4.59 (2H, s), 4.54 (2H, s), 3.80 (6H, s), 3.22 (1H, m), 2.96 (3H, m), 2.75 (1H, m), 1.16 (3H, d) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 550, $[M+Na]^+$ 572.

Example 10 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl]-*N*-(2-benzyloxy-6-methoxybenzyl)-1H-indole-2-carboxamide



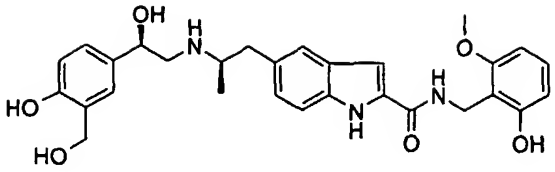
Prepared using the amide from Preparation **10** and the method described for Example **1**.

^{1}H NMR (400MHz, CD_3OD) : δ = 7.74 (1H, bd), 7.36 (6H, m), 7.15 (1H, bd), 6.96 (3H, m), 6.86 (1H, d), 6.73 (1H, d), 6.68 (1H, d), 6.58 (1H, d), 5.16 (2H, s), 4.72 (2H, s), 4.59 (1H, m), 4.54 (2H, s), 3.87 (3H, s), 3.87 (3H, s), 2.893 (2H, m), 2.70 (3H, m), 1.09 (3H, d) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 610, $[M+Na]^+$ 632.

Example 11 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl]-*N*-(2-hydroxy-6-methoxybenzyl)-1H-indole-2-

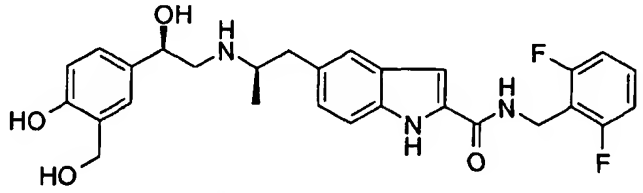
carboxamide



Prepared using the ether from Example **10** and the method described for Example **9**.

^{1}H NMR (400MHz, $DMSO_{d6}$) : δ = 11.45 (1H, s), 9.99 (1H, bs), 9.14 (1H, bs), 8.62 (1H, bs), 7.31 (1H, s), 7.28 (1H, d), 7.22 (1H, d), 7.12 (1H, s), 7.08 (1H, t), 6.96 (2H, dt), 6.65 (1H, d), 6.36 (2H, t), 4.94 (2H, m), 4.42 (5H, m), 3.77(3H, s), 2.82-2.73 (2H, m), 2.60 (1H, d), 2.43 (1H, m), 0.89 (3H, d) ppm.
LRMS (ESI) : m/z $[M+H]^+$ 520, $[M+Na]^+$ 542.

Example 12 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl]-*N*-(2,6-difluorobenzyl)-1H-indole-2-carboxamide



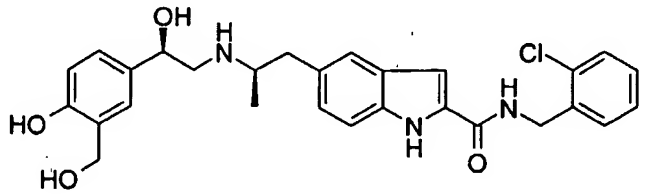
The acid from Preparation **11** (145 m g, 292 μmol) in DMF (1 ml) was treated with 2,6-difluorobenzylamine (43 mg, 301 μmol), pyridine (26 mg, 325 μmol), HOBt (43 mg, 320 μmol) in DMF (1ml) and WSCDI (62 mg, 322 μmol) in DMF (1 ml) and the mixture shaken overnight. The solvent was removed *in vacuo* and replaced with DCM (2ml) and water (0.5 ml). The organic phase was separated using a PTFE frit cartridge and the solvent removed *in vacuo*. Ammonium fluoride (108 mg, 292 μmol) in MeOH (1.9 ml) and water (1.1 ml) was added to the crude material and the mixture shaken at 40 °C overnight. The solvent was removed *in vacuo* and the crude material taken up in DMSO (1 ml) and filtered before being purified by reverse phase HPLC.

^{1}H NMR (400MHz, CD_3OD): δ =7.49 (1H, s), 7.44-7.42 (1H, d), 7.39-7.32 (2H, m), 7.15-7.11 (2H, m), 7.06 (1H, s), 7.02-6.94 (2H, m), 6.78-6.76 (1H, d), 4.87

(1H, partially obscured by solvent), 4.68 (2H, s), 4.65 (2H, s), 3.61-3.54 (1H, m), 3.26-3.12 (3H, m), 2.87-2.81 (1H, m), 1.26-1.25 (3H, d) ppm.

HRMS (ESI) : m/z $[M+H]^+$ found 510.2178; requires 510.2199.

Example 13 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(2-chlorobenzyl)-1H-indole-2-carboxamide

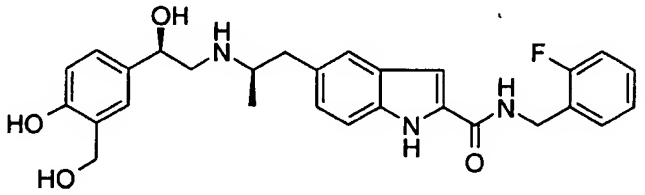


Prepared using the acid from Preparation **11** and the method described for Example **12**.

^{1}H NMR (400MHz, CD_3OD): δ = 7.52 (1H, s), 7.46-7.40 (3H, m), 7.34 (1H, s), 7.29-7.26 (2H, m), 7.15-7.13 (3H, m), 6.78-6.76 (1H, d), 4.89 (1H, partially obscured by solvent), 4.69 (2H, s), 4.65 (2H, s), 3.63-3.55 (1H, m), 3.28-3.113 (3H, m), 2.89-2.83 (1H, m), 1.28-1.26 (3H, d) ppm.

HRMS (ESI) : m/z $[M+H]^+$ found 508.1979; requires 508.1998.

Example 14 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(2-fluorobenzyl)-1H-indole-2-carboxamide

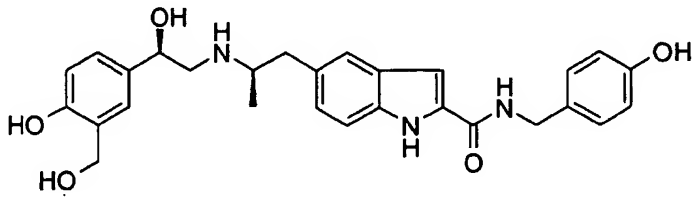


Prepared using the acid from Preparation **11** and the method described for Example **12**.

^{1}H NMR (400MHz, CD_3OD): δ =7.51 (1H, s), 7.45-7.40 (2H, m), 7.37-7.26 (2H, m), 7.16-7.07 (5H, m), 6.78-6.76 (1H, d), 4.88 (1H, partially obscured by solvent), 4.66-4.64 (4H, m), 3.63-3.54 (1H, m), 3.27-3.13 (3H, m), 288-2.82 (1H, m), 1.27-1.26 (3H, d) ppm.

HRMS (ESI) : m/z $[M+H]^+$ found 492.2274; requires 492.2293.

Example 15 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(4-hydroxybenzyl)-1H-indole-2-carboxamide

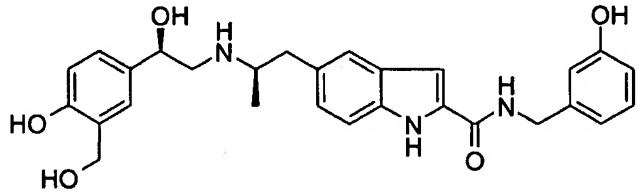


Prepared using the acid from Preparation **11** and the method described for Example **12.**

^{1}H NMR (400MHz, CD_3OD): δ =7.50 (1H, s), 7.44 (1H, d), 7.34 (1H, s), 7.19 (2H, d), 7.15-7.11 (2H, m), 7.06 (1H, s), 6.78-6.73 (3H, m), 4.88 (1H, partially obscured by solvent), 4.65 (2H, s), 4.48 (2H, s), 3.61-3.53 (1H, m), 3.27-3.13 (3H, m), 2.88-2.82 (1H, m), 1.27-1.26 (3H, d) ppm.

HRMS (ESI) : m/z $[M+H]^+$ found 490.2321; requires 490.2337.

Example 16 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(3-hydroxybenzyl)-1H-indole-2-carboxamide

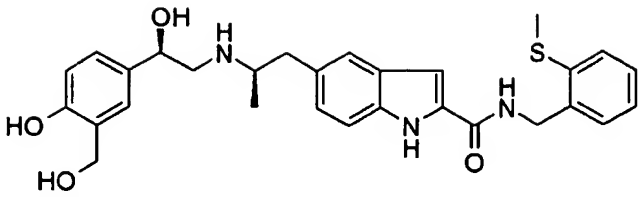


Prepared using the acid from Preparation **11** and the method described for Example **12.**

^{1}H NMR (400MHz, CD_3OD): δ =7.51 (1H, s), 7.46-7.43 (1H, d), 7.34 (1H, s), 7.16-7.03 (4H, m), 6.83-6.76 (3H, m), 6.68-6.66 (1H, d), 4.90 (1H, partially obscured by solvent), 4.65 (2H, s), 4.53 (2H, s), 3.63-3.54 (1H, m), 3.27-3.13 (3H, m), 2.88-2.82 (1H, m), 1.27-1.26 (3H, d) ppm.

HRMS (ESI) : m/z $[M+H]^+$ found 490.2319; requires 490.2337.

Example 17 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(2-methylsulfanylbenzyl)-1H-indole-2-carboxamide

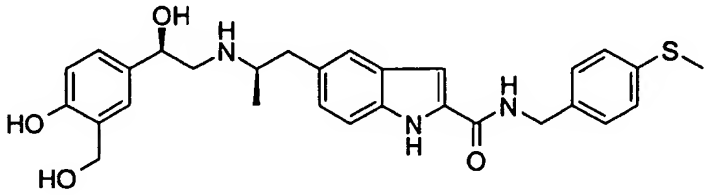


Prepared using the acid from Preparation **11** and the method described for Example **12**, using 2 equivalents of pyridine.

^{1}H NMR (400MHz, CD_3OD): δ =7.52 (1H, s), 7.45-7.43 (1H, d), 7.35-7.26 (4H, m), 7.17-7.11 (4H, m), 6.77 (1H, d), 4.88 (1H, partially obscured by solvent), 4.66-4.65 (4H, m), 3.63-3.55 (1H, m), 3.27-3.13 (3H, m), 2.88-2.83 (1H, m), 2.50 (3H, s), 1.27 (3H, d) ppm.

HRMS (ESI) : m/z $[M+H]^+$ found 520.2246; requires 520.2265.

Example 18 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl]-*N*-(4-methylsulfanylbenzyl)-1H-indole-2-carboxamide

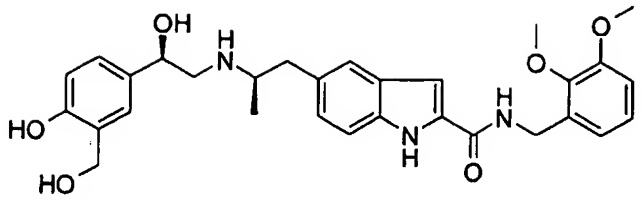


Prepared using the acid from Preparation **11** and the method described for Example **12**.

^{1}H NMR (400MHz, CD_3OD): δ =7.51 (1H, s), 7.44 (1H, d), 7.34-7.29 (3H, m), 7.25-7.23 (2H, m), 7.15-7.12 (2H, m), 7.07 (1H, s), 6.77 (1H, d) 4.88 (1H, partially obscured by solvent), 4.65 (2H, s), 4.55 (2H, s), 3.61-3.56 (1H, m), 3.27-3.12 (3H, m), 2.88-2.82 (1H, m), 2.45 (3H, s), 1.27-1.26 (3H, d) ppm.

HRMS (ESI) : m/z $[M+H]^+$ found 520.2245; requires 520.2265.

Example 19 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl]-*N*-(2,3-dimethoxybenzyl)-1H-indole-2-carboxamide

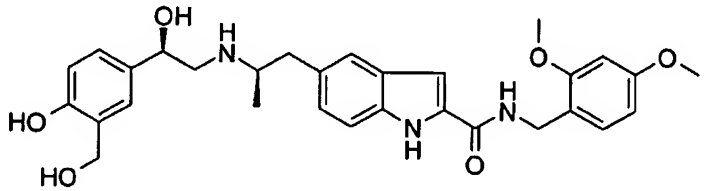


Prepared using the acid from Preparation **11** and the method described for Example **12**.

^{1}H NMR (400MHz, CD_3OD): δ = 7.51 (1H, s), 7.44 (1H, d), 7.34 (1H, s), 7.15-7.12 (2H, m), 7.09 (1H, s), 7.05-6.99 (1H, m), 6.96-6.92 (2H, m), 6.77 (1H, d), 4.88 (1H, partially obscured by solvent), 4.65 (2H, s), 4.62 (2H, s), 3.86 (3H, s), 3.85 (3H, s), 3.61-3.55 (1H, m), 3.27-3.13 (3H, m), 2.88-2.82 (1H, m), 1.27-1.26 (3H, d) ppm.

HRMS (ESI) : m/z $[M+H]^+$ found 534.2579; requires 534.2599.

Example 20 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(2,4-dimethoxybenzyl)-1H-indole-2-carboxamide

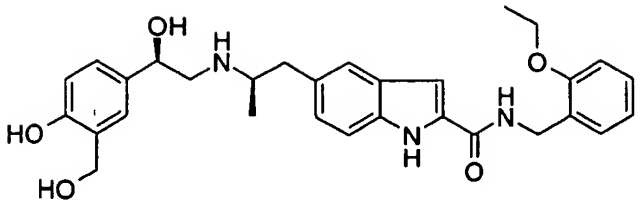


Prepared using the acid from Preparation **11** and the method described for Example **12**.

^{1}H NMR (400MHz, CD_3OD): δ = 7.50 (1H, s), 7.43 (1H, d), 7.34 (1H, s), 7.19 (1H, d), 7.15-7.09 (2H, m), 7.07 (1H, s), 6.77 (1H, d), 6.55 (1H, s), 6.51-6.44 (1H, m), 4.89 (1H, partially obscured by solvent), 4.65 (2H, s), 4.51 (2H, s), 3.85 (3H, s), 3.78 (3H, s), 3.62-3.56 (1H, m), 3.27-3.13 (3H, m), 2.88-2.82 (1H, m), 1.27-1.26 (3H, d) ppm.

HRMS (ESI) : m/z $[M+H]^+$ found 534.2577; requires 534.2599.

Example 21 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(2-ethoxybenzyl)-1H-indole-2-carboxamide

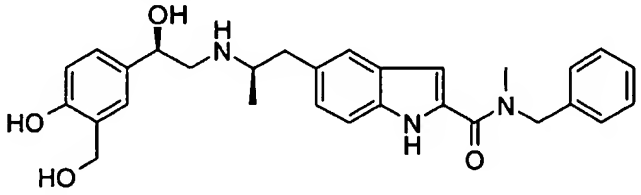


Prepared using the acid from Preparation **11** and the method described for Example **12**.

^{1}H NMR (400MHz, CD_3OD): δ = 7.51 (1H, s), 7.44 (1H, d), 7.34 (1H, s), 7.28-7.20 (2H, m), 7.15-7.12 (2H, m), 7.09 (1H, s), 6.96-6.94 (1H, d), 6.91-6.87 (1H, t), 6.78 (1H,), 4.89 (1H, partially obscured by solvent), 4.65 (2H, s), 4.61 (2H, s), 4.10 (2H, q), 3.62-3.56 (1H, m), 3.27-3.13 (3H, m), 2.88-2.82 (1H, m), 1.44-1.40 (3H, t), 1.28-1.26 (3H, d) ppm.

HRMS (ESI) : m/z $[M+H]^+$ found 518.2631; requires 518.2650.

Example 22 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-benzyl-*N*-methyl-1H-indole-2-carboxamide

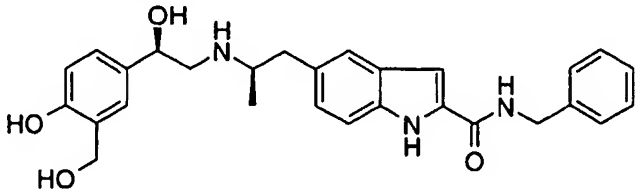


Prepared using the acid from Preparation **11** and the method described for Example **12**.

^{1}H NMR (400MHz, CD_3OD): δ = 7.54-7.27 (9H, m), 7.14-7.12 (2H, m), 6.77 (1H, d), 5.08-4.92 (1H, m), 4.90 (2H, partially obscured by solvent), 4.64 (2H, s), 3.61-3.53 (1H, m), 3.28-3.05 (6H, m), 2.87-2.81 (1H, m), 1.26-1.25 (3H, d) ppm.

LRMS (APCI) : m/z $[M+H]^+$ 488, $[M-H]^-$ 486.

Example 23 : [(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-benzyl-1H-indole-2-carboxamide

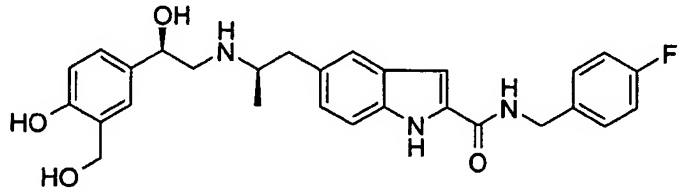


Prepared using the acid from Preparation **11** and the method described for Example **12**.

^{1}H NMR (400MHz, CD_3OD): δ = 7.51 (1H, s), 7.44 (1H, d), 7.38-7.30 (5H, m), 7.26-7.23 (1H, m), 7.15-7.12 (2H, m), 7.08 (1H, s), 6.78-6.76 (1H, d), 4.88 (1H, partially obscured by solvent), 4.65 (2H, s), 4.59 (2H, s), 3.61-6.56 (1H, m), 3.27-3.13 (3H, m), 2.88-2.82 (1H, m), 1.27 (3H, s) ppm.

HRMS (ESI) : m/z $[M+H]^+$ found 474.2370; requires 474.2388.

Example 24 : [(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(4-fluorobenzyl)-1H-indole-2-carboxamide

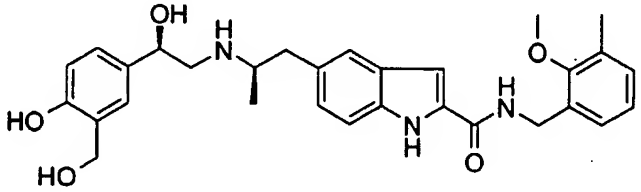


Prepared using the acid from Preparation **11** and the method described for Example **12**.

^{1}H NMR (400MHz, CD_3OD): δ = 7.88 (1H, d), 7.74 (1H, d), 7.33-7.57 (7H, m), 7.13 (2H, m), 7.05 (2H, t), 6.77 (1H, d), 4.85 (1H, m), 4.65 (2H, s), 4.56 (2H, s), 3.54-3.62 (1H, m), 3.13-3.27 (3H, m), 2.81-2.88 (1H, m), 1.27 (3H, d) ppm.

HRMS (ESI) : m/z $[M+H]^+$ found 492.2275; requires 492.2300.

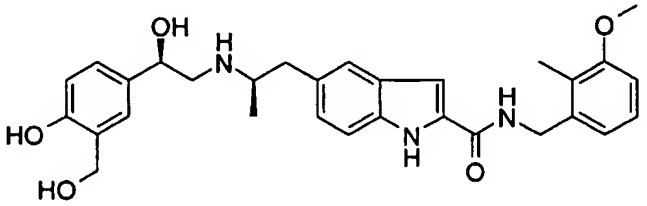
Example 25 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(2-methoxy-3-methyl-benzyl)-1H-indole-2-carboxamide



Prepared using the acid from Preparation **46** and the method described for Example **12**.

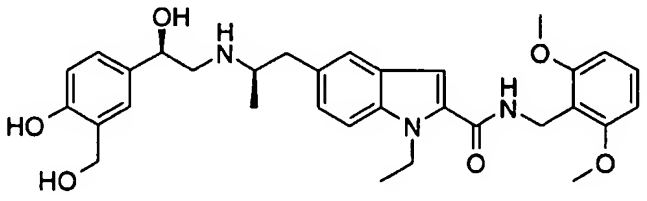
^{1}H NMR (400MHz, CD_3OD): δ = 7.44 (1H, s), 7.38 (1H, d), 7.27(1H, s), 7.17 (1H, d), 7.12-7.05 (4H, m), 6.99 (1H, t), 6.70 (1H, d), 4.65 (2H, s), 4.61(3H, s), 3.80 (3H, s), 3.12-2.95(4H, m), 2.79 (1H, m), 2.30 (3H, s), 1.19 (3H, d) ppm.
HRMS (ESI) : m/z $[M+H]^+$ found 518.2650, $C_{30}H_{36}N_3O_5$ requires 518.2646

Example 26 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(3-methoxy-2-methylbenzyl)-1H-indole-2-carboxamide



Prepared using the acid from Preparation **45** and the method described for Example **12**.
^{1}H NMR (400 MHz, CD_3OD) : δ = 7.56 (2H, d), 7.15 (1H, d), 7.09 (1H, d), 7.01-6.95 (4H, m), 6.83 (1H, d), 6.60 (1H, d) 4.59 (2H, s), 4.55 (2H, s), 3.80 (3H, s), 3.01-2.95(2H, m), 2.80-2.62 (3H, m), 2.25 (3H, s), 1.13 (3H, d) ppm.
LRMS (ESI) : m/z $[M+H]^+$ 518.63

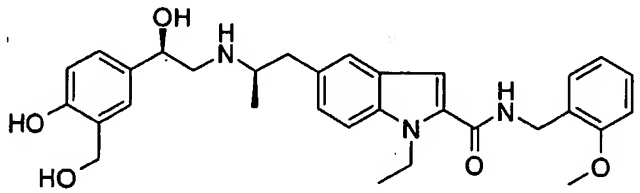
Example 27 : 1-Ethyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl}amino)propyl}-*N*-(2,6-dimethoxybenzyl)-1H-indole-2-carboxamide



Prepared using the acid from Preparation **31** and the method described for Example **12**.
^{1}H NMR (400 MHz, CD_3OD) : δ = 7.31-7.24 (3H, m), 7.16 (1H, bs), 7.02-6.96 (2H, m), 6.75-6.58 (4H, m), 4.64-4.50 (7H, m), 3.86 (6H, s), 2.99-2.91 (2H, m), 2.74-2.67 (3H, m), 1.33 (3H, t), 1.11 (3H, d) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 562, $[M+Na]^+$ 584.

Example 28 : 1-Ethyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl}amino)propyl]-*N*-(2-ethoxybenzyl)-1H-indole-2-carboxamide

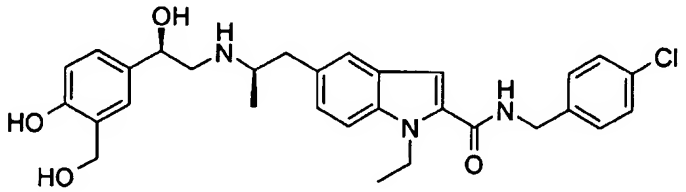


Prepared using the amide from Preparation **31** and the method described for Example **12**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.32-7.23 (4H, m), 7.16 (1H, bs), 7.03-6.89 (5H, m), 6.60 (1H, d), 4.61-4.50 (7H, m), 3.87 (3H, s), 2.96-2.89 (2H, m), 2.73-2.65 (3H, m), 1.32 (3H, t), 1.10 (3H, d) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 532, $[M+Na]^+$ 554.

Example 29 : 1-Ethyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl}amino)propyl]-*N*-(4-chlorobenzyl)-1H-indole-2-carboxamide

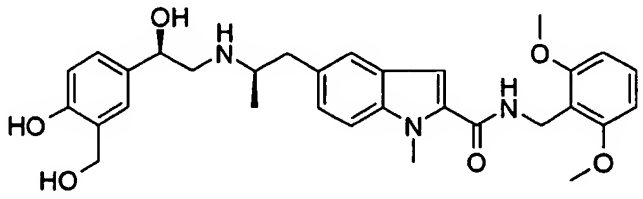


Prepared using the amide from Preparation **31** and the method described for Example **12**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.37-7.30 (6H, m), 7.16 (1H, bs), 7.04-7.01 (1H, m), 6.97-6.95 (2H, m), 6.60 (1H, d), 4.60-4.49 (7H, m), 2.96-2.88 (2H, m), 2.72-2.64 (3H, m), 1.32 (3H, t), 1.10 (3H, d) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 536, $[M+Na]^+$ 558.

Example 30 : 1-Methyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl}amino)propyl}-*N*-(2,6-dimethoxybenzyl)-1H-indole-2-carboxamide

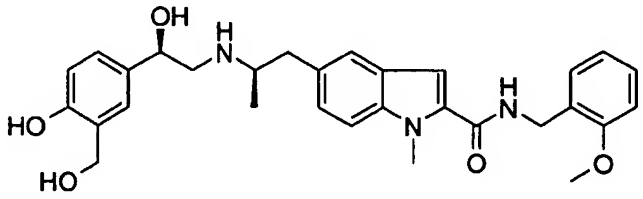


Prepared using the amide from Preparation **26** and the method described for Example **12**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.28-7.24 (3H, m), 7.13 (1H, bs), 7.00 (1H, d), 6.91 (1H, d), 6.77 (1H, s), 6.65 (2H, d), 6.53 (1H, d), 4.65 (2H, s), 4.59-4.56 (1H, m), 4.49 (2H, s), 3.96 (3H, s), 3.87 (6H, s), 2.98-2.92 (2H, m), 2.72-2.63 (3H, m), 1.11 (3H, m) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 548, $[M+Na]^+$ 570.

Example 31 : 1-Methyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl}amino)propyl}-*N*-(2-methoxybenzyl)-1H-indole-2-carboxamide

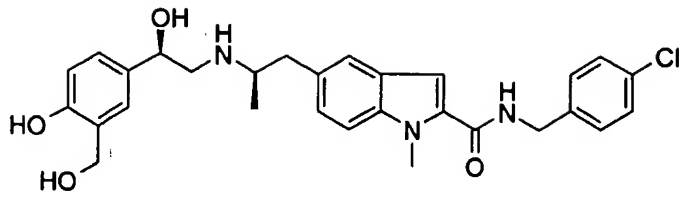


Prepared using the amide from Preparation **26** and the method described for Example **12**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.32-7.24 (4H, m), 7.12 (1H, bs), 7.02-6.89 (5H, m), 6.53 (1H, d), 4.58-4.53 (3H, m), 4.49 (2H, s), 3.97 (3H, s), 3.89 (3H, s), 2.95-2.88 (2H, m), 2.75-2.59 (3H, m), 1.12-1.10 (3H, m) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 518, $[M+Na]^+$ 540.

Example 32 : 1-Methyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl}amino)propyl}-*N*-(4-chlorobenzyl)-1H-indole-2-carboxamide

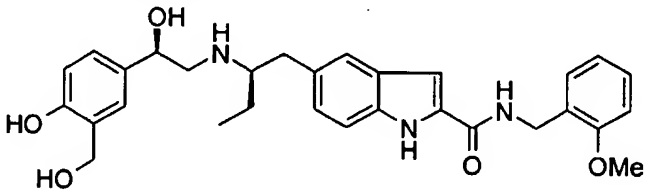


Prepared using the amide from Preparation **26** and the method described for Example **12**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.39-7.27 (6H, m), 7.11 (1H, bs), 7.02 (1H, d), 6.95 (1H, s), 6.91 (1H, d), 6.54 (1H, d), 4.57-4.54 (3H, m), 4.49 (2H, s), 3.99 (3H, s), 2.95-2.89 (2H, m), 2.77-2.60 (3H, m), 1.11 (3H, d) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 522, $[M+Na]^+$ 544

Example 33 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)butyl]-*N*-(2-methoxybenzyl)-1H-indole-2-carboxamide

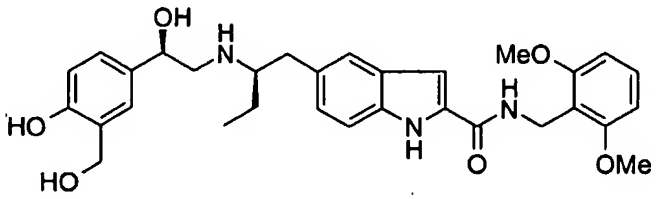


A solution of Preparation **40** (158 mg, 220 μmol) in ethanol (10 ml) was treated with ammonium formate (70 mg, 1.1 mmol) and palladium hydroxide on carbon (10 mg) and heated to reflux for 2 h. Ammonium fluoride (40 mg, 1.1 mmol) in water (1 ml) was then added and the resulting mixture stirred at 40 °C for 24 h. The solvents were then removed and the crude material taken up in ethyl acetate, washed with water (containing 1 % 0.88 ammonia) and dried (Na_2SO_4). The product was purified by chromatography (2-5 % MeOH in CH_2Cl_2 and 0.3 % NH_3) to yield a colourless solid (66 mg).

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.38-7.15 (5H, m), 7.04-6.88 (5H, m), 6.60-6.54 (1H, d), 4.59 (2H, s), 4.58-4.52 (3H, m), 3.86 (3H, s), 2.89-2.59 (5H, m), 1.61-1.39 (2H, m), 0.98-0.94 (3H, t) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 518, $[M+Na]^+$ 540.

Example 34 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)butyl]-*N*-(2,6-dimethoxybenzyl)-1H-indole-2-carboxamide

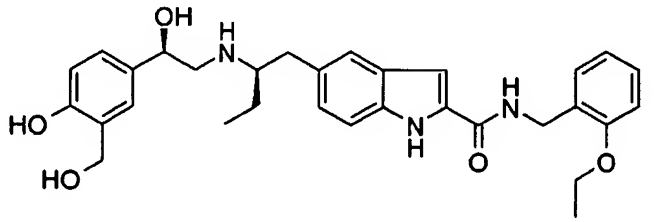


Prepared using the ether from Preparation **41** and the method described for Example **33**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.38-7.12 (4H, m), 6.98-6.90 (3H, m), 6.68-6.65 (2H, d), 6.58-6.56 (1H, d), 4.66 (2H, s), 4.58-4.53 (3H, m), 3.86 (6H, s), 2.88-2.59 (5H, m), 1.60-1.38 (2H, m), 0.98-0.93 (3H, t) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 548, $[M+Na]^+$ 570.

Example 35 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)butyl]-*N*-(2-ethoxybenzyl)-1H-indole-2-carboxamide

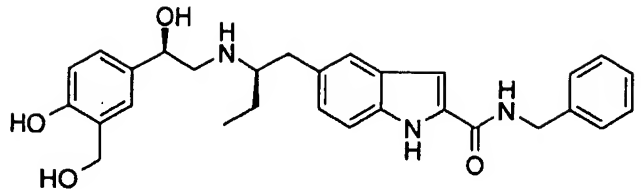


Prepared using the ether from Preparation **42** and the method described for Example **33**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.35-7.16 (5H, m), 7.04-6.88 (5H, m), 6.58-6.56 (1H, d), 4.61 (2H, s), 4.58-4.52 (3H, m), 4.15-4.06 (2H, q), 2.90-2.59 (5H, m), 1.62-1.40 (5H, m), 0.98-0.93 (3H, t) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 532, $[M+Na]^+$ 554.

Example 36 : 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)butyl]-*N*-benzyl-1H-indole-2-carboxamide



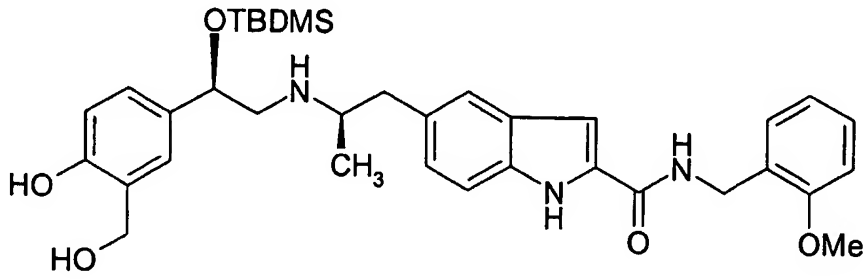
Prepared using the ether from Preparation **39** and the method described for Example **33**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.41-6.92 (11H, m), 6.58-6.56 (1H, d), 4.59 (2H, s), 4.57-4.51 (3H, m), 2.88-2.58 (5H, m), 1.62-1.38 (2H, m), 0.98-0.92 (3H, t) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 488, $[M+Na]^+$ 510.

The following Preparations describe the preparation of certain intermediates used in the preceding Examples.

PREPARATION 1 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(2-methoxy benzyl)-1*H*-indole-2-carboxamide



A solution of 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylic acid (Preparation 11, 0.25 g, 0.50 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (106 mg, 0.55 mmol), hydroxybenzotriazole (75 mg, 0.55 mmol) in N, N-dimethylformamide (5 ml) was treated with triethylamine (0.15 ml, 0.55 mmol) and 2-methoxybenzylamine (0.07 ml, 0.55 mmol) and the resulting suspension left to stir at room temperature under

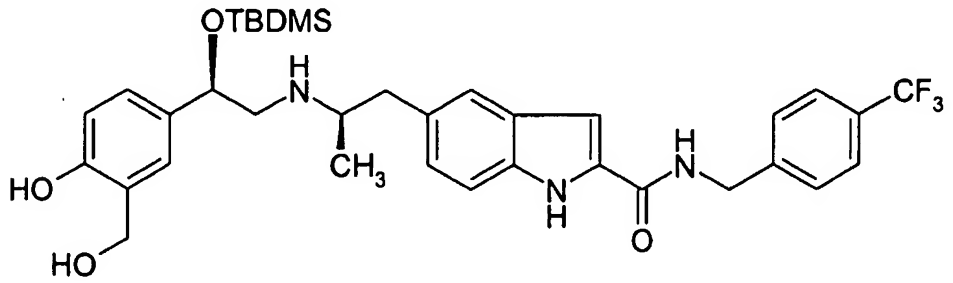
a nitrogen atmosphere for 18 hours. The solvent was removed in vacuo and the residue partitioned between dichloromethane (50 ml) and saturated aqueous sodium bicarbonate (20 ml). The organic phase was separated, dried (sodium sulphate) and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol (95:5 changing to 90:10, by volume) to give the title compound as a colourless foam (76 mg).

^{1}H NMR (400MHz, CD_3OD): δ = 7.35-7.23 (4H, m), 7.16 (1H, s), 7.05 (1H, s), 7.01-6.89 (4H, m), 6.62-6.59 (1H, d), 4.70-4.67 (1H, t), 4.60-4.57 (4H, m), 3.89 (3H, s), 3.01-2.96 (1H, m), 2.93-2.88 (1H, m), 2.75-2.61 (3H, m), 1.11-1.10 (3H, d), 0.73 (9H, s), -0.08 (3H, s), -0.25 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 618.

Analysis : Found C 66.98; H 7.67; N 6.70; $C_{35}H_{47}N_3O_5Si$. $0.5H_2O$ requires C 67.06; H 7.72; N 6.70.

Preparation 2 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-[4-(trifluoromethyl)benzyl]-1*H*-indole-2-carboxamide

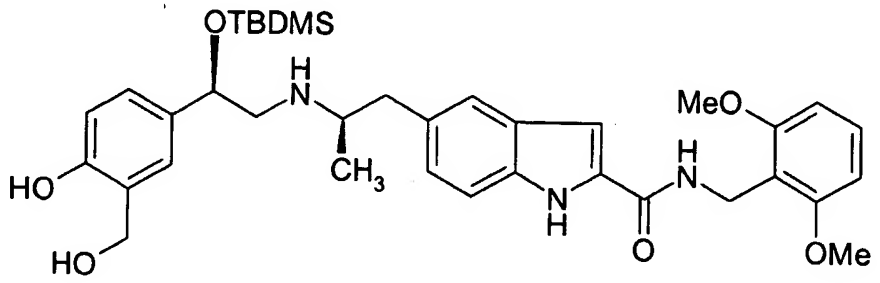


Prepared analogously to 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(2-methoxybenzyl)-1*H*-indole-2-carboxamide using 4-trifluoromethylbenzylamine to give the title compound as a pale brown foam.

^{1}H NMR (400MHz, CD_3OD): δ = 7.65-7.63 (2H, m), 7.57-7.55 (2H, m), 7.40-7.38 (2H, m), 7.21 (1H, s), 7.08-7.04 (2H, m), 6.99-6.97 (1H, d), 6.67-6.65 (1H, d), 4.80-4.77 (1H, m), 4.68 (2H, s), 4.64-4.57 (2H, m), 3.08-3.02 (2H, m), 2.86-2.78 (3H, m), 1.18-1.17 (3H, d), 0.74 (9H, s), -0.05 (3H, s), -0.23 (3H,s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 656.

Preparation 3 : 5-[(2*R*)-2-{{(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(2,6-dimethoxy benzyl)-1*H*-indole-2-carboxamide

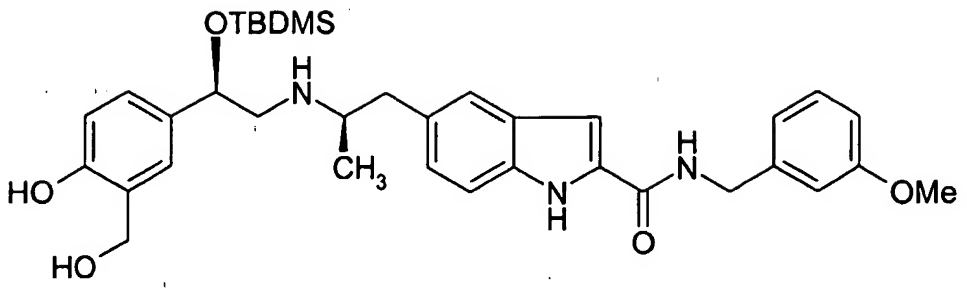


Prepared analogously to 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(2-methoxybenzyl)-1*H*-indole-2-carboxamide using 2,6-dimethoxybenzylamine to give the title compound as a pale yellow foam.

^{1}H NMR (400MHz, CD_3OD): δ = 7.35-7.28 (3H, m), 7.18 (1H, bs), 7.02-6.95 (3H, m), 6.71 (2H, d), 6.63 (1H, d), 4.70-4.68 (3H, m), 4.62-4.56 (2H, m), 3.90 (6H, s), 3.00-2.89 (2H, m), 2.72-2.62 (3H, m), 1.11 (3H, d), 0.76 (9H, s), -0.05 (3H, s), -0.22 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 648, $[M+Na]^+$ 670.

Preparation 4 : 5-[(2*R*)-2-{{(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(3-methoxybenzyl)-1*H*-indole-2-carboxamide



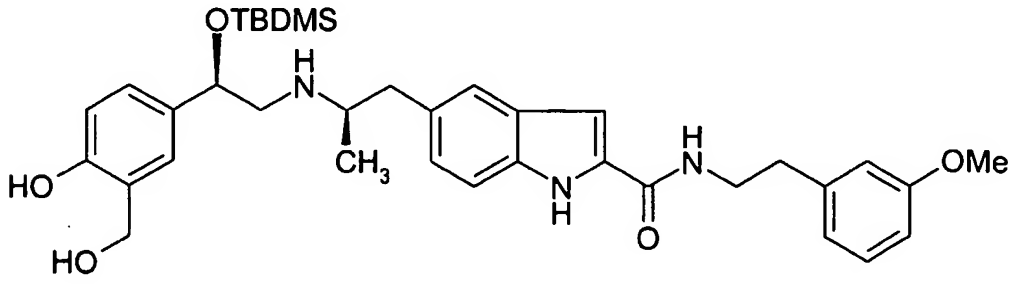
Prepared analogously to 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(2-methoxybenzyl)-1*H*-indole-2-carboxamide using 3-methoxybenzylamine to give the title compound as a pale brown foam.

^{1}H NMR (400MHz, CD_3OD): δ = 7.36-7.34 (2H, m), 7.25-7.21 (1H, t), 7.17 (1H, s), 7.05-7.00 (2H, m), 6.95-6.94 (3H, m), 6.82-6.80 (1H, m), 6.62-6.60 (1H, d), 4.71-4.68 (1H, m), 4.62-4.54 (4H, m), 3.77 (3H, s), 3.02-2.90 (2H, m), 2.73-2.64 (3H, m), 1.12-1.10 (3H, d), 0.71 (9H, s), -0.09 (3H, s), -0.26 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 618.

Analysis : Found C 66.45; H 7.57; N 6.63; $C_{35}H_{47}N_3O_5Si$. $0.85H_2O$ requires C 66.39; H 7.75; N 6.64.

Preparation 5 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-[2-(3-methoxyphenyl)ethyl]-1*H*-indole-2-carboxamide



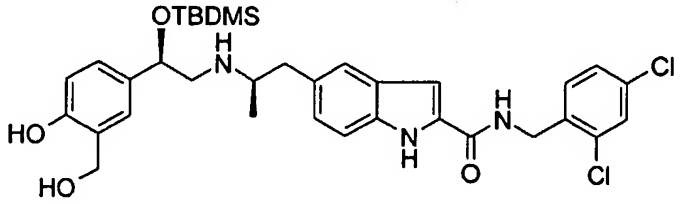
Prepared analogously to 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(2-methoxybenzyl)-1*H*-

indole-2-carboxamide using 3-methoxyphenethylamine to give the title compound as a pale brown foam.

^{1}H NMR (400MHz, CD_3OD): δ = 7.35-7.33 (2H, m), 7.20-7.16 (2H, m), 7.02-6.99 (1H, m), 6.95-6.93 (2H, m), 6.84-6.83 (2H, m), 6.77-6.74 (1H, m), 6.63-6.61 (1H, d), 4.73-4.71 (1H, m), 4.62-4.55 (2H, m), 3.74 (3H, s), 3.62-3.59 (2H, t), 3.09-3.04 (1H, m), 2.98-2.85 (4H, m), 2.76-2.68 (2H, m), 1.13-1.12 (3H, d), 0.72 (9H, s), -0.08 (3H, s), -0.25 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 632.

Preparation 6 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(2,4-dichloro benzyl)-1*H*-indole-2-carboxamide

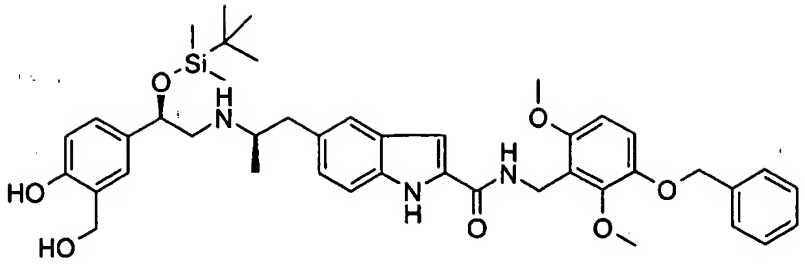


Prepared using the acid from Preparation **11** and the method described for Preparation **1**.

^{1}H NMR (400MHz, CD_3OD): δ = 7.47 (1H, s), 7.42 (1H, m), 7.33-7.29 (3H, m), 7.15 (1H, s), 7.07 (1H, s), 7.00 (1H, d), 6.93 (1H, d), 6.60 (1H, d), 4.67 (13H, m), 4.60-4.53 (2H, m), 2.98 (1H, m), 2.90 (1H, m), 2.73 (2H, m), 2.63 (1H, m), 1.10 (3H, d), 0.72 (9H, s), -0.09 (3H, s), -0.26 (3H, s)

LRMS (APCI) : m/z $[M]^+$ 656.

Preparation 7 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(3-benzyloxy-2,6-dimethoxybenzyl)-1*H*-indole-2-carboxamide

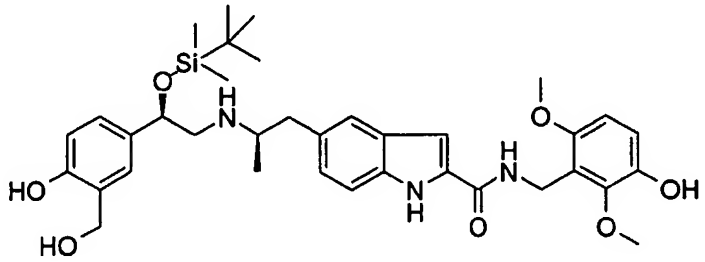


Prepared using the acid from Preparation **11**, the amine from Preparation **59** and the method described for Preparation **1**.

^{1}H NMR (400MHz, $CDCl_3$): δ = -0.21 (3H, s), -0.05 (3H, s), 0.78 (9H, s), 1.10 (3H, bs), 2.55-2.95 (3H, m), 3.85 (3H, s), 3.98 (3H, s), 4.60 (3H, s), 4.78 (2H, d), 5.10 (2H, s), 6.50-6.70 (3H, m), 6.78-6.98 (5H, m), 7.27-7.43 (6H, m), 9.15 (1H, s).

LRMS (electrospray) : m/z $[M+H]^+$, 754, $[M+Na]^+$, 776.

Preparation 8 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(3-hydroxy-2,6-dimethoxy benzyl)-1*H*-indole-2-carboxamide

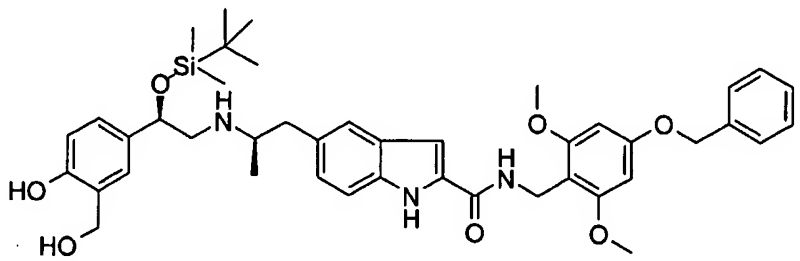


Preparation **7** (137 mg, 182 μmol) was hydrogenated with palladium on carbon (10%, 20 mg) at 50 psi for 12 h at 30 °C. The reaction mixture was filtered through a filter-aid and the solvent removed. The crude material was then purified by chromatography (0-7 % MeOH in CH_2Cl_2 and 1 % ammonia) to yield a clear glass (73 mg).

^{1}H NMR (400MHz, CD_3OD): δ = -0.27 (3H, s), -0.10 (3H, s), 0.72 (9H, s), 1.09 (3H, m), 2.69 (3H, m), 3.13 (2H, m), 3.34 (3H, m), 3.81 (3H, s), 3.85 (3H, s), 4.56 (1H, d), 4.65 (2H, bs), 4.92 (3H, m), 6.59 (1H, d), 6.62 (1H, d), 6.80 (1H, d), 6.93 (1H, d), 6.97 (2H, s), 6.99 (1H, s), 7.15 (1H, s), 7.30 (2H, m) ppm.

LRMS (electrospray) : m/z $[M+H]^+$, 664, $[M+Na]^+$, 696.

Preparation 9 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(4-benzyloxy-2,6-dimethoxybenzyl)-1*H*-indole-2-carboxamide

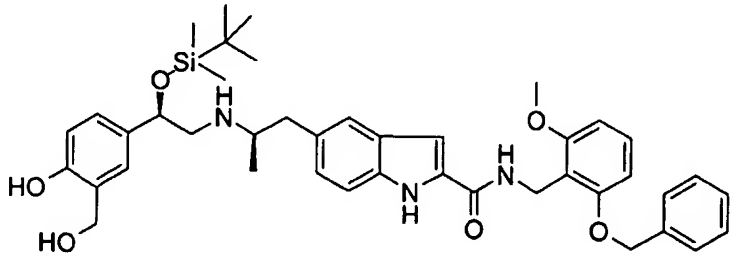


Prepared using the acid from Preparation **11**, the amine from Preparation **49** and the method described for Preparation **1**.

^1H NMR (400MHz, $CDCl_3$): δ = -0.24 (3H, s), -0.07 (3H, s), 0.75 (9H, s), 10.6 (3H, d), 2.53 (1H, m), 2.68 (2H, m), 2.86 (2H, m), 3.83 (6H, s), 4./60 (3H, bs), 4.69 (2H, d), 5.06 (2H, s), 6.23 (2H, s), 6.60 (3H, m), 6.76 (1H, s), 6.93 (2H, t), 7.26 (1H, m), 7.33-7.45 (6H, m), 9.38 (1H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$, 754, $[M+Na]^+$, 776.

Preparation 10 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-*N*-(2-benzyloxy-6-methoxybenzyl)-1*H*-indole-2-carboxamide



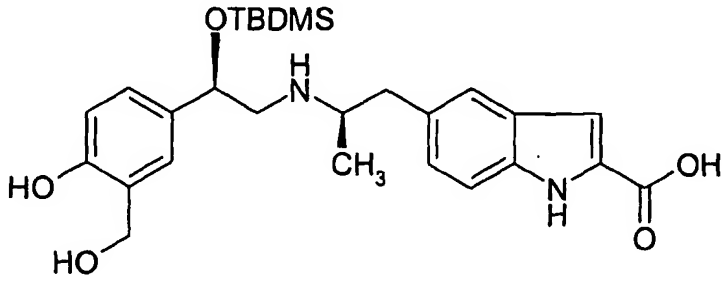
Prepared using the acid from Preparation **11**, the amine from Preparation **52** and the method described for Preparation **1**.

^1H NMR (400MHz, $CDCl_3$): δ = -0.23 (3H, s), -0.06 (3H, s), 0.76 (9H, s), 1.07 (3H, d), 2.54 (1H, m), 2.68 (2H, m), 2.86 (2H, m), 3.38 (3H, s), 4.60 (1H, s), 4.84 (2H, s), 5.15 (2H, s), 6.43 (1H, s), 6.60 (1H, t), 6.67 (1H, d), 6.76 (1H, d),

6.82 (1H, t), 6.94 (2H, d), 7.23 (2H, m), 7.34-7.41 (3H, m), 7.48 (2H, m), 9.26 (1H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$, 724, $[M+Na]^+$, 746.

Preparation 11 : 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylic acid

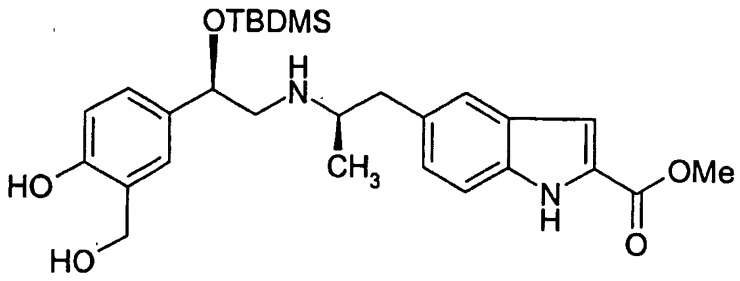


A solution of methyl 5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylate (Preparation 12, 0.30 g, 0.59 mmol) in 1,4-dioxane (10 ml) was treated with a solution of sodium hydroxide (59 mg, 1.46 mmol) in water (1 ml) and the resulting mixture left to stir at room temperature for 30 minutes. After this time the reaction mixture was heated to 90°C for 30 minutes and then cooled to room temperature. The solvent was removed in vacuo and the residue re-dissolved in water (20 ml) and pH adjusted to 7 by addition of 2N Hydrochloric acid. The solid that formed was filtered off, solubilised in a mixture of dichloromethane and methanol (20 ml 90:10 by volume), dried (magnesium sulphate) and the solvent removed in vacuo to give the title compound as a pale orange foam.

^{1}H NMR (400MHz, CD_3OD): δ = 7.47-7.42 (2H, m), 7.27 (1H, s), 7.11-7.03 (3H, m), 6.76-6.74 (1H, d), 4.99-4.97 (1H, m), 4.67-4.58 (2H, m); 3.60-3.55 (1H, m), 3.28-3.26 (1H, m), 3.16-3.12 (1H, m), 3.09-3.04 (1H, m), 2.94-2.88 (1H, m), 1.28-1.26 (3H, d), 0.74 (9H, s), -0.03 (3H, s), -0.22 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$, 499.

Preparation 12: Methyl 5-[(2*R*)-2-{{(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylate



A suspension of methyl 5-{(2*R*)-2-[((2*R*)-2-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino]propyl}-1*H*-indole-2-carboxylate (Preparation 13, 0.38 g, 0.63 mmol) and 10% palladium on carbon (78 mg) in ethanol (20 ml) was stirred under an atmosphere of hydrogen (60psi) at room temperature for 16 hours. The catalyst was filtered off through arbocel and the solvent removed in vacuo to give the title compound as a pale pink foam (316 mg), which was used without further purification.

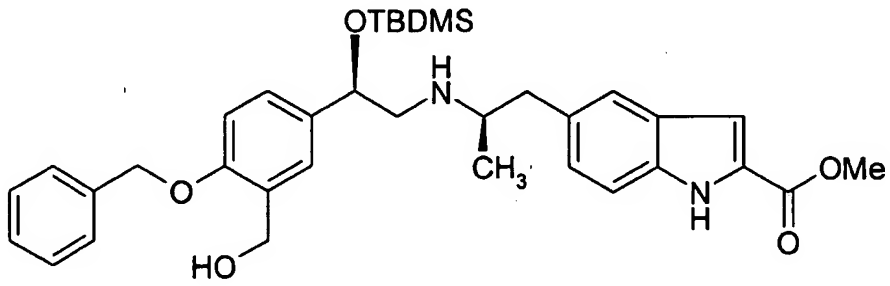
^{1}H NMR (400MHz, CD_3OD): δ = 7.36-7.32 (2H, m), 7.15 (1H, bs), 7.09 (1H, bs), 7.05-7.04 (1H, m), 6.95-6.93 (1H, m), 6.62 (1H, d), 4.69-4.66 (1H, m), 4.57 (2H, s), 3.92 (3H, s), 2.98-2.85 (2H, m), 2.70 (2H, d), 2.63-2.59 (1H, m), 1.08 (3H, d), 0.71 (9H, s), -0.09 (3H, s), -0.26 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$513, $[M+Na]^+$ 535.

Analysis : Found C 64.89; H 7.93; N 5.08; $C_{28}H_{40}N_2O_5Si$. 0.25H_2O requires C 65.02; H 7.89; N 5.42

Optical Rotation $[\alpha]^D_{25}$ = -84.02° 0.4mg/ml MeOH 635nm

Preparation 13 : Methyl 5-{(2*R*)-2-[((2*R*)-2-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino] propyl}-1*H*-indole-2-carboxylate



A solution of methyl 5-[(2*R*)-2-aminopropyl]-1*H*-indole-2-carboxylate (Preparation 14, 5.00 g, 21.5 mmol) and [2-(benzyloxy)-5-((1*R*)-2-bromo-1-{[*tert*-butyl(dimethyl)silyl] oxy}ethyl)phenyl]methanol (Preparation 20, 4.86 g, 10.8 mmol) in dichloromethane (50 ml) was heated to 90°C allowing the dichloromethane to evaporate gradually. The resulting melt was left at 90°C for 16h under nitrogen. The reaction mixture was then cooled to room temperature and the resulting solid triturated with dichloromethane. The solid was filtered off and the solvent removed in vacuo to give a pale orange oil. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia (99:1:0.1 by volume) to give the title compound as a pale yellow oil (3.90 g).

^{1}H NMR (400MHz, CD_3OD): δ = 7.44-7.27 (8H, m), 7.08-7.04 (2H, m), 6.96-6.93 (1H, m), 6.67 (1H, d), 4.98 (2H, s), 4.72-4.67 (1H, m), 4.60 (2H, s), 3.82 (3H, s), 2.99-2.89 (2H, m), 2.77-2.72 (1H, m), 2.65-2.59 (2H, m), 1.11 (3H, d), 0.74 (9H, s), -0.07 (3H, s), -0.24 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$603, $[M+Na]^+$ 625.

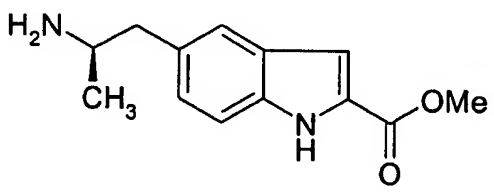
Analysis : Found C 69.26; H 7.72; N 4.61; $C_{35}H_{46}N_2O_5Si$. $0.2H_2O$ requires C 69.32; H 7.71; N 4.62

Alternative process:

In a 4 l reactor, 200 g of Methyl 5-[(2*R*)-2-aminopropyl]-1*H*-indole-2-carboxylate hydrochlorid were dissolved in 830 ml of dimethylformamide, and 411 g of potassium carbonate and 123.3 g of KI were then added. 334.1 g of [2-(benzyloxy)-5-((1*R*)-2-bromo-1-{[*tert*-butyl(dimethyl) silyl]oxy}ethyl) phenyl] methanol, dissolved in 500 ml of MTBE, were added to this mixture. The resulting suspension was stirred vigorously at an internal temperature of about 80°C - 82°C for about 26 hours. During stirring, about 80 ml of MTBE were distilled off. After cooling to room temperature, the suspension was filtered off with suction, and the residue on the frit was washed twice with in each case 100 ml of DMF. The combined organic filtrates were, with vigorous stirring, introduced into a mixture of 1.2 kg of ice, 3.8 l of deionized water and 1.6 l of toluene. After about 15 minutes of stirring, the mixture was allowed to stand for about 15 min for phase separation. The slightly turbid organic phase was separated off and the likewise turbid aqueous phase was reextracted with 1 l of toluene.

The combined toluene phases are then washed with 1.6 l of water, twice with in each case 370 ml of 0.1 N hydrochloric acid and with 500 ml of a saturated sodium chloride solution. The organic phase was filtered and dried over 170 g of Na_2SO_4.The dried toluene solution was concentrated under reduced pressure to a volume of about 700 ml. Under reduced pressure the mixture was then co-distilled 4 times with in each case 250 ml of methanol, where initially about 500 ml and then about 300 ml and twice in each case about 250 ml of solvent were distilled off. The red oily residue that remains could, after being dissolved in MeOH (4 l), be used directly for the hydrogenation in the next step.

Preparation 14 : Methyl 5-[(2*R*)-2-aminopropyl]-1*H*-indole-2-carboxylate



A solution of methyl 5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino}propyl)-1*H*-indole-2-carboxylate (Preparation 15, 9.34 g, 25.0 mmol) in ethanol (125 ml) was treated with ammonium formate (7.90 g, 125 mmol) and palladium hydroxide on carbon (2.81 g, 20% b/w palladium). The resulting suspension was purged with nitrogen and then heated to reflux for an hour. The reaction mixture was cooled to room temperature and filtered through arbocel to remove catalyst residues. The filtrate was reduced in vacuo and the residue was partitioned between 0.88 ammonia (100 ml) and dichloromethane (100 ml). The organic phase was separated and the aqueous extracted with more dichloromethane (100 ml). The combined organic extracts were dried (sodium sulphate) and the solvent removed in vacuo to give the title compound as a colourless oil (6.25 g, trace solvent remaining by ^{1}H NMR).

^{1}H NMR (400MHz, CD_3OD): δ = 7.44 (1H, bs), 7.36 (1H, d), 7.13 (1H, d), 7.11 (1H, s), 3.90 (3H, s), 3.17-3.07 (1H, m), 2.77-2.61 (2H, m), 1.10 (3H, d) ppm.

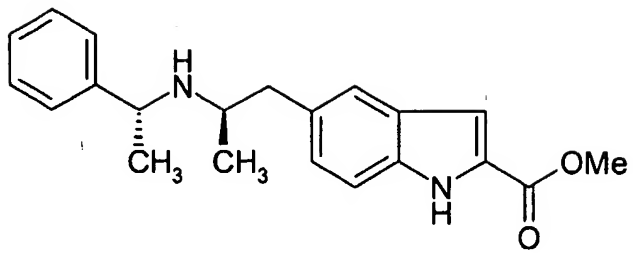
LRMS (electrospray) : m/z $[M+H]^+$ 233, $[M+Na]^+$ 255.

Optical Rotation $[\alpha]^D_{25}$ = -22.58° 6.76mg/ml MeOH 589nm

Alternative process: Methyl 5-[(2*R*)-2-aminopropyl]-1*H*-indole-2-carboxylate hydrochlorid

203 g of Methyl 5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino}propyl)-1*H*-indole-2-carboxylate hydrochloride were hydrogenated over $Pd(OH)_2/C$ at about 80°C and 5 bar for a period of 30 min. After cooling to room temperature, the catalyst was filtered off, and the clear filtrate was concentrated under reduced pressure at about 50°C to dryness.

Preparation 15 : Methyl 5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino}propyl)-1*H*-indole-2-carboxylate



A solution of 1-*tert*-butyl 2-methyl 5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino}propyl)-1*H*-indole-1,2-dicarboxylate (Preparation 16, 20.48 g, 46.9 mmol) was treated with 4M hydrogen chloride in methanol and the resulting solution left to stir at room temperature for 16 hours and then heated at 50°C for a further 2 hours. The solvent was removed in vacuo to give a solid which was crystallised from a mixture of methanol (125 ml) and diisopropylether (50 ml) to give the title compound as a colourless crystalline solid (9.34 g, d.e.>98% as determined by ^{1}H NMR).

^{1}H NMR (400MHz, CD_3OD): δ = 7.53-7.49 (5H, m), 7.40-7.38 (2H, m), 7.10, 1H, bs), 6.97 (1H, bd), 4.61 (1H, q), 3.91 (3H, s), 3.42-3.37 (1H, m), 3.26-3.19 (1H, m), 2.72-2.66 (1H, m), 1.69 (3H, d), 1.19 (3H, d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 337.

Alternative process: Methyl 5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino}propyl)-1*H*-indole-2-carboxylate hydrochloride

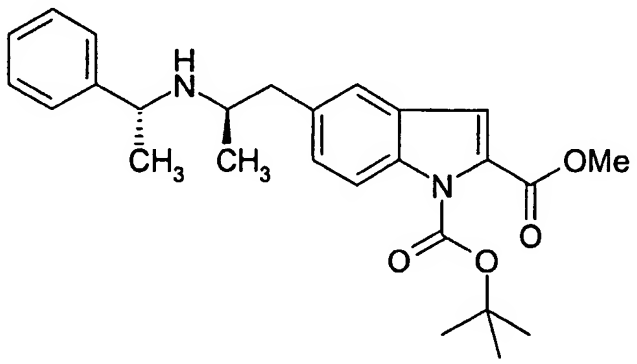
7.79 l of toluene and 1.416 l of methanol were initially charged in a 20 l reactor. The mixture was cooled to about -6°C. Over a period of 70 min, 2242 ml of acetyl chloride were added dropwise such that the temperature in the reactor increases from -6°C to 2°C. The reaction mixture was stirred for about 20 min, and a solution of 779 g of 1-*tert*-butyl 2-methyl 5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino}propyl)-1*H*-indole-1,2-dicarboxylate in 1046 ml of toluene was then added dropwise over a period of about 55 min such that the temperature in the reactor remains between 4°C - 10°C.

About 10 min after the end of the addition, the product begins to crystallize out. Over a period of about 1.5 hours, the temperature in the reaction mixture was

allowed to increase to 16°C - 17°C. At this temperature, the reaction mixture was stirred under a gentle stream of N_2 for 20 hours (overnight). The reaction mixture was cooled to about 0°C, stirred at this temperature for 1 hour and then filtered off with suction. The filter cake was washed 3 times with in each case 520 ml of cold (5°C) toluene.

The filter cake was dried in a fresh air drying cabinet at 50°C until the weight remains constant (clear crystals).

Preparation 16 : 1-*tert*-butyl 2-methyl 5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino}propyl)-1*H*-indole-1,2-dicarboxylate



A solution of 1-*tert*-butyl 2-methyl 5-(2-oxopropyl)-1*H*-indole-1,2-dicarboxylate (18.0 g, 54.32 mmol), (R)-α-methyl benzylamine (Preparation 17, 6.4 ml, 49.65 mmol), sodium triacetoxyborohydride (15.80 g, 74.55 mmol) and acetic acid (3.0 ml, 52.38 mmol) in dichloromethane (500 ml) was stirred at room temperature for 16 hours. The reaction mixture was quenched by addition of saturated aqueous sodium bicarbonate (200 ml) and allowed to stir until effervescence ceased. The organic phase was separated and the aqueous phase extracted with further dichloromethane (100 ml). The combined organic extracts were dried (magnesium sulphate) and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane : methanol : 0.88 ammonia (99:1:0.1 changing to 98:2:0.2, by volume) to give a 4:1 mixture of diastereomers (*R*,*R* major) as a pale yellow oil (20.48 g).

^{1}H NMR (400MHz, CD_3OD): δ = 7.97-7.92 (1H, m), 7.41-7.02 (8H, m), 4.04-3.99 (1H, m), 3.96-3.94 (3H, m), 3.15-3.10 (1H, m), 2.80-2.70 (1H, m), 2.53-2.48 (1H, m), 1.66 (9H, s), 1.39-1.31 (3H, 2d), 1.10-0.95 (3H, 2d) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 437.

Alternative process:

In a 20 l reactor, , 1259.6 g of 1-*tert*-butyl 2-methyl 5-(2-oxopropyl)-1*H*-indole-1,2-dicarboxylate were dissolved in 7.28 l of toluene, and 408.98 g of R-(+)-α-methylbenzylamine were then added dropwise (about 3 min) at room temperature.

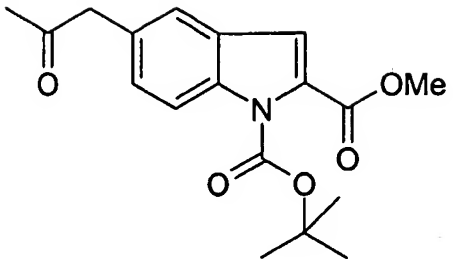
A solution of 226.33 g of glacial acetic acid in 220 ml of toluene was added dropwise over a period of about 30 min (exothermic) such that the temperature in the reactor does not exceed 20°C. Over a period of about 15 min, 1079.5 g of sodium triacetoxyborohydride were added a little at a time to the suspension such that the temperature in the reactor does not exceed 20°C. The reaction mixture was stirred at room temperature for about 6 hours.

Initially, about 6.33 l of a 5% strength $NaHCO_3$ solution were added to the reaction mixture such that the temperature remains below 20°C (pH = 5). After about 30 minutes of stirring, the aqueous phase was separated. The organic phase was once more stirred with 6.33 l of a 5% strength $NaHCO_3$ solution for about 30 min (pH = 8) and the aqueous phase was separated.

The combined aqueous phases were reextracted with 4 l of toluene. The combined organic phases were washed with 1.74 l of water. The toluene phase was filtered, and the solvent and the water contained therein were distilled off from the clear solution under reduced pressure.

What remains was a dark oil which was used for the next step without further purification.

Preparation 17 : 1-*tert*-butyl 2-methyl 5-(2-oxopropyl)-1*H*-indole-1,2-dicarboxylate

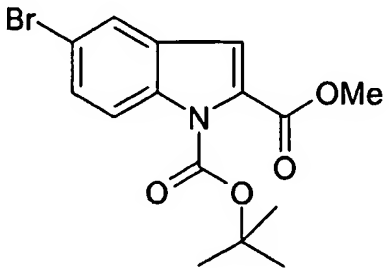


A solution of 1-*tert*-butyl 2-methyl 5-bromo-1*H*-indole-1,2-dicarboxylate (Preparation 18, 12.5 g, max 32.04 mmol), tributyltin methoxide (11.0 ml, 38.2 mmol), isoprenylacetate (5.3 ml, 48.1 mmol), palladium acetate (0.36 g, 5 mol%), tri-o-tolylphosphine (0.97 g, 10 mol%) in toluene (40 ml) was degassed and then heated at 100°C for 8 hours. The reaction mixture was diluted with ethyl acetate (50 ml), 4M potassium fluoride (aqueous, 100 ml) and left to stir at room temperature overnight. The resulting mixture was filtered through arbocel washing the precipitate thoroughly with ethyl acetate (100 ml) and the organic phase of the filtrate separated, dried (magnesium sulphate) and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica gel eluting with pentane:ethyl acetate (95:5 changing to 90:10, by volume) to give the title compound (8.2 g) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.05 (1H, d), 7.44 (1H, s), 7.25 (1H, d), 7.05 (1H, s), 3.92 (3H, s), 3.78 (2H, s), 2.16 (3H, s), 1.61 (9H, s) ppm.

LRMS (electrospray) : m/z $[M-H]^-$ 330, $[M+Na]^+$ 354.

Preparation 18 : 1-*tert*-butyl 2-methyl 5-bromo-1*H*-indole-1, 2-dicarboxylate



A solution of methyl 5-bromo-1*H*-indole-2-carboxylate (Preparation 19, 8.14 g, 32.04 mmol) in tetrahydrofuran (300 ml) was added to sodium hydride (1.35 g of a 40% dispersion in mineral oil, 33.7 mmol) at 0°C under nitrogen. The resulting mixture was left to stir until effervescence ceased (50 minutes). A solution of di-*tert*-butyldicarbonate in further tetrahydrofuran (30 ml) was added to the reaction and the resulting mixture stirred vigorously, warming gradually to room temperature overnight. The solvent was removed in vacuo and the residue partitioned between ethyl acetate (200 ml) and water (200 ml). The organic phase was separated and the aqueous extracted with more ethyl acetate (2-fold 200 ml). The combined organics were dried (magnesium sulphate) and the solvent removed in vacuo to give the title compound as a pale yellow oil (12.5 g – trace solvent remaining).

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.98 (1H, d), 7.74 (1H, s), 7.50 (1H, dd), 7.00 (1H, s), 3.92 (3H, s), 1.61 (9H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 352 / 354, $[M+Na]^+$ 376 / 378.

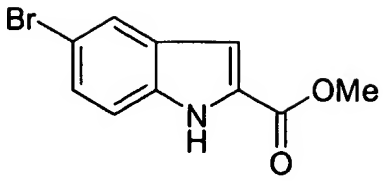
Alternative process:

5953 l of toluene, 926.26 g of Methyl 5-bromo-1*H*-indole-2-carboxylate and 35.80 g of DMAP were initially charged in a 20 l reactor. At about 20°C, a solution comprising 856.63 g of Boc_2O and 1209 l of toluene was added dropwise to the suspension over a period of about 1 hour.The reaction mixture was stirred at about 20°C for about 2 hours.

The reaction mixture was stirred once with 2.787 l of a 1M citric acid solution, once with 2.787 l of a semi-concentrated $NaHCO_3$ solution and finally once with 2.787 l of a semi-concentrated NaCl solution.

The toluene phase was separated and dried over 232 g of sodium sulphate. The mixture was filtered and the solvent was distilled off from the clear solution under reduced pressure at 40°C.

Preparation 19 : Methyl 5-bromo-1*H*-indole-2-carboxylate



A solution of 5-Bromo-1*H*-indole-2-carboxylic acid (commercial, 10.0 g, 41.6 mmol) in methanol (200 ml) was cooled to 0°C and saturated with HCl(g). The resulting solution was allowed to warm gradually to room temperature overnight. The solvent was removed in vacuo and the residue treated with 0.88 ammonia (500 ml). The resulting solution was extracted with dichloromethane (3-fold 150 ml) and the combined organics dried (magnesium sulphate) and the solvent removed in vacuo to give the required product as a colourless oil (8.35 g).

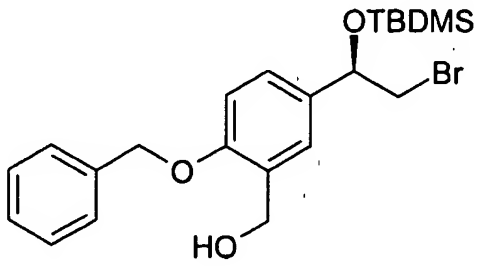
^{1}H NMR (400MHz, $CDCl_3$): δ = 8.96 (1H, bs), 7.83 (1H, s), 7.40 (1H, d), 7.30 (1H, d), 7.14 (1H, s), 3.95 (3H, s) ppm.

LRMS (electrospray) : m/z $[M-H]^-$ 252 / 254.

Alternative process:

At room temperature and under a stream of N_2, 9.12 l of methanol and 910 g of 5-bromoindole-2-carboxylic acid were initially charged in a 20 l reactor. The suspension was cooled to about 0°C. With vigorous stirring, 881 ml of acetyl chloride were added dropwise with cooling over a period of about 55 min such that the temperature in the reactor does not exceed 5°C. The suspension was then heated to 60°C and the reaction mixture was stirred at 60°C for about 6 hours. The reaction mixture was allowed to cool to room temperature (overnight). At 480 mbar - 500 mbar, 4.76 l of methanol were then distilled off. The thick slurry that remains was still readily stirrable. The suspension was cooled to about 0°C and stirred at this temperature for about 1 hour. The precipitate was filtered off with suction and the filter cake was washed 3 times with in each case 400 ml of methanol. The product, thoroughly washed, was dried in a fresh air drying cabinet at 50°C until the weight remains constant.

Preparation 20 : [2-(benzyloxy)-5-((1*R*)-2-bromo-1-{[*tert*-butyl(dimethyl) silyl]oxy}ethyl) phenyl]methanol



Borane methylsulfide complex (42.4 ml of ~10M solution, 424 mmol) was added drop wise to a solution of methyl 2-(benzyloxy)-5-((1*R*)-2-bromo-1-{[*tert*-butyl(dimethyl) silyl]oxy} ethyl)benzoate (Preparation 21, 91.0 g) in tetrahydrofuran (1600 ml).The resulting mixture was then heated to reflux for 2 hours and then cooled to 0°C before quenching with methanol (270 ml). The mixture was left to stir at room temperature for 16 hours and then the solvent removed in vacuo. The residue was partitioned between dichloromethane (500 ml) and water (500 ml). The aqueous phase was separated and extracted with more dichloromethane (500 ml) and the combined organic extracts washed with saturated aqueous sodium chloride (500 ml), dried (magnesium sulphate) and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica gel eluting with cyclohexane:ethyl acetate (100:0 changing to 80:20, by volume) to give the title compound (68.7 g) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.42-7.36 (5H, m), 7.29-7.25 (3H, m), 6.94 (1H, d), 5.12 (2H, s), 4.84-4.81 (1H, m), 4.74 (2H, s), 3.48-3.40 (2H, m), 0.90 (9H, s), 0.11 (3H, s), -0.07 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 473 / 475.

Alternative process: At room temperature and under a stream of N_2, 1381 g of methyl 2-(benzyloxy)-5-((1*R*)-2-bromo-1-{[*tert*-butyl(dimethyl) silyl]oxy}

ethyl)benzoate were dissolved in 6.4 l of THF in a reactor. The reaction solution was heated to about 45°C. Over a period of 2 hours, 6.4 l of the 1M BH_3/THF complex in THF were added dropwise at a steady rate such that the temperature in the reactor remains between 47°C - 50°C.

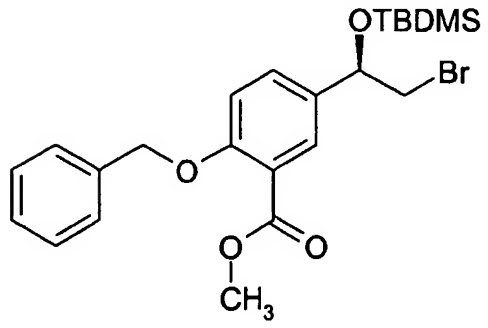
The reaction mixture was stirred at 50°C for about 6 hours.

The reaction solution was then cooled to about 10°C. To decompose excess BH_3 or BH complexes, 1280 ml of an MeOH/THF mixture (1:1) were slowly added over a period of about 2hours such that the temperature in the reactor does not exceed 10°C.

The reaction solution is concentrated under reduced pressure at 40°C. To remove residual amounts of solvents, the mixture was concentrated further at 40 mbar and 40°C. The oily residue was dissolved in 8 l of MTBE and washed 3 times with in each case 3.2 l of water.

Since the organic phase is slightly turbid, it was dried over 400 g of Na_2SO_4. The mixture was filtered, and the solvent was distilled off from the clear solution under reduced pressure. What remains was a honey-coloured syrup.

Preparation 21 : Methyl 2-(benzyloxy)-5-((1*R*)-2-bromo-1-{[*tert*-butyl(dimethyl)silyl]oxy} ethyl)benzoate



At room temperature and under a stream of N_2, 2.334 l of DMF and 933.67 g of methyl 5-acetylsalicylate were initially charged in a 20 l reactor. 695.2 g of potassium carbonate were then added. At about 23°C, 860.4 g (600 ml) of benzyl bromide were added dropwise with stirring over a period of about 12 min. The reaction mixture was then heated at about 45°C for about 45 min. The reaction mixture was stirred at 45°C for about 5 hours. The reaction mixture was cooled to about 15°C, and a total of 8.72 l of demineralized water

were added with stirring at this temperature over a period of about 33 min. The suspension was stirred at room temperature for about another 2.5 hours. The precipitate was filtered off with suction and the filter cake was washed twice with in each case 1.86 l of water. The filter cake was then washed with a total of 2.8 l of the water/2-propanol mixture (1:1). The filter cake was dried in a fresh air drying cabinet at 50°C until the weight remains constant.

At room temperature and under a stream of N_2, 1.18 l of methanol and 5.01 l of abs. THF were initially charged in a 20 l reactor. 1226.89 g of 5-Acetyl-2-benzyloxy-benzoic acid methyl ester are introduced into this mixture. 2184.85 g of tetra-n-butylammonium tribromide were dissolved in 3.79 l of abs. THF. With vigorous stirring, this solution was added dropwise over a period of about 3.5 hours. After addition of about 4.5 l of the bromide solution, a product begins to precipitate. After the addition, 11.8 l of water were added dropwise over a period of about 1 hour with vigorous stirring such that the temperature in the reactor remains between 15°C - 20°C. The precipitated product was filtered off with suction and washed 3 times with in each case 1.77 l of water. Then, the filter cake was sucked thoroughly dry and washed twice with in each case 1.77 l of tert-butyl methyl ether. The filter cake was dried in a fresh air drying cabinet at 50°C until the weight remains constant.

Under reduced pressure, the solvent was distilled off at about 40°C. The oily residue was dissolved in 2 l of ethyl acetate and then stirred with 1 l of water and 500 ml of 2N hydrochloric acid. After phase separation, the organic phase was washed twice with in each case 500 ml of water, once with 500 ml of a 5% strength $NaHCO_3$ solution and finally with 500 ml of a 5% strength sodium chloride solution. After drying over 100 g of Na_2SO_4, the organic phase was filtered, and the solvent was distilled off completely under reduced pressure at about 40°C. The oily residue was taken up in 1167 ml of 2-propanol. To remove remaining ethyl acetate, about 600 ml of 2-propanol were distilled off under reduced pressure at about 40°C. With stirring, the distillate was replaced by about 600 ml of fresh 2-propanol. The mixture was allowed to cool to room temperature (about 20°C) and stirred at this temperature for several hours. The

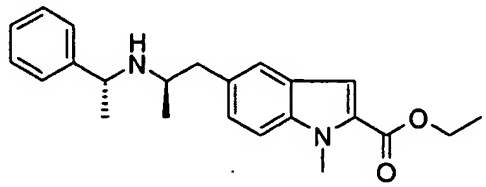
precipitated product was filtered off with suction and washed 7 times thoroughly with in each case 50 ml of ice-cold 2-propanol. The filter cake was dried in a fresh air drying cabinet at about 50°C until the weight remains constant.

A solution of methyl 2-(benzyloxy)-5-[(1*R*)-2-bromo-1-hydroxyethyl]benzoate (71.05 g, 195 mmol), imidazole (18.52 g, 272 mmol), *tert*-butyldimethylsilyl chloride (32.23 g, 214 mmol) and 4-(dimethylamino)pyridine (0.44 g, 3.6 mmol) in DMF (270 ml) was left to stir at room temperature under a nitrogen atmosphere for a period of 24 hours. The solvent was removed in vacuo and the residue partitioned between ethyl acetate (500 ml) and water (500 ml). The organic phase was separated and washed with 2N hydrochloric acid (2-fold 500 ml), saturated aqueous sodium bicarbonate (2-fold 500 ml) saturated sodium chloride (500 ml), dried (magnesium sulphate) and the solvent removed in vacuo to give the title compound as a colourless oil (91.0 g).

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.81 (1H, bs), 7.51-7.30 (6H, m), 7.01 (1H, d), 5.19 (2H, s), 4.85-4.82 (1H, m), 3.91 (3H, s), 3.48-3.39 (2H, m), 0.90 (9H, s), 0.11 (3H, s), -0.08 (3H, s) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 501 / 503.

Preparation 22 : Ethyl 1-methyl-5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino}propyl)-1*H*-indole-2-carboxylate



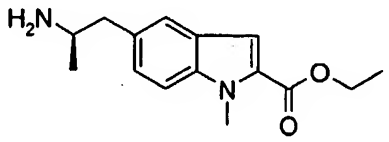
Prepared using the procedure of Preparation **15**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.56-7.48 (5H, m), 7.43-7.40 (2H, m), 7.19 (1H, s), 7.04 (1H, d), 4.62 (1H, q), 4.35 (2H, q), 4.03 (3H, s), 3.45-3.40 (1H, m),

3.28-3.21 (1H, m), 2.74-2.69 (1H, m), 1.70 (3H, d), 1.39 (3H, t), 1.19 (3H, d) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 635, $[M+Na]^+$ 387.

Preparation 23 : Ethyl 1-methyl-5-[(2*R*)-2-aminopropyl]-1*H*-indole-2-carboxylate

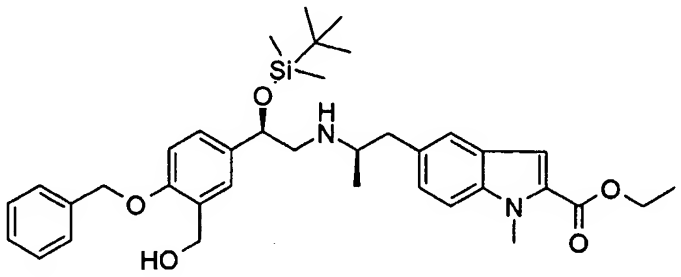


Prepared using the amine from Preparation **22** and the method described for Preparation **14**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.46-7.40 (2H, m), 7.22-7.19 (2H, m), 4.35 (2H, q), 4.04 (3H, s), 3.18-3.10 (1H, m), 2.77-2.65 (2H, m), 1.39 (3H, t), 1.10 (3H, d) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 261, $[M+Na]^+$ 283.

Preparation 24 : Ethyl 1-methyl-5-{(2*R*)-2-[((2*R*)-2-[4-(benzyloxy)-3-(hydroxymethyl) phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino]propyl}-1*H*-indole-2-carboxylate

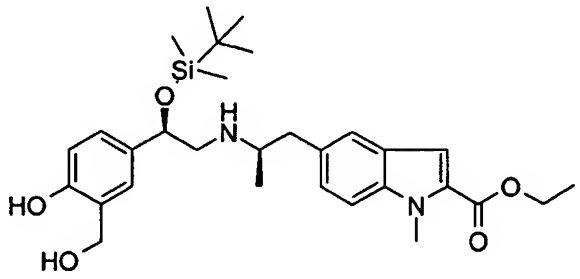


Prepared using the amine from Preparation **23**, and the bromide from preparation **21** and the method described for Preparation **14**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.43-7.26 (8H, m), 7.18 (1H, bs), 7.10 (1H, d), 6.98 (1H, d), 6.72 (1H, d), 4.99 (2H, s), 4.71-4.68 (1H, m), 4.58 (2H, s), 4.29 (2H, q), 4.01 (3H, s), 2.98-2.90 (2H, m), 2.78-2.73 (1H, m), 2.65-2.58 (2H, m), 1.36 (3H, t), 1.11 (3H, d), 0.73 (9H, s), -0.07 (3H, s), -0.24 (3H, s) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 631, $[M+Na]^+$ 653.

Preparation 25 : Ethyl 1-methyl-5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylate

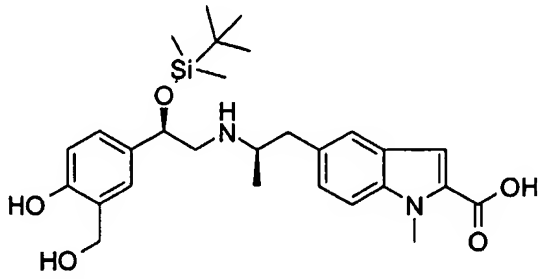


Prepared using the ester from Preparation **24** and the method described for Preparation **12**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.35-7.31 (2H, m), 7.18 (1H, s), 7.11-7.06 (2H, m), 6.92 (1H, d), 6.58 (1H, d), 4.66-4.63 (1H, m), 4.53 (2H, s), 4.37 (2H, q), 4.05 (3H, s), 2.96-2.87 (2H, m), 2.76-2.56 (3H, m), 1.40 (3H, t), 1.10 (3H, d), 0.72 (9H, s), -0.08 (3H, s), -0.26 (3H, s) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 541, $[M+Na]^+$ 563.

Preparation 26 : 1-Methyl-5-[(2*R*)-2-({(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylic acid

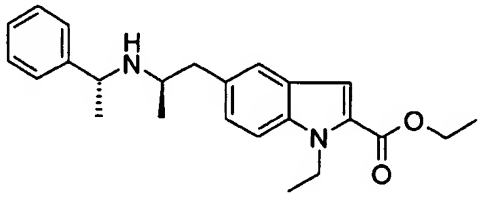


Prepared using the ester from Preparation **25** and the method described for Preparation **11**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.44-7.39 (2H, m), 7.25 (1H, s), 7.16-7.00 (3H, m), 6.72 (1H, d), 4.99-4.96 (1H, m), 4.64-4.56 (2H, m), 4.02 (3H, s), 3.60-3.54 (1H, m), 3.13-2.89 (4H, m), 1.27-1.26 (3H, m), 0.72 (9H, s), -0.04 (3H, s), -0.24 (3H, s) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 513, $[M+Na]^+$ 535.

Preparation 27 : Ethyl 1-ethyl-5-((2*R*)-2-{[(1*R*)-1-phenylethyl]amino} propyl)-1*H*-indole-2-carboxylate

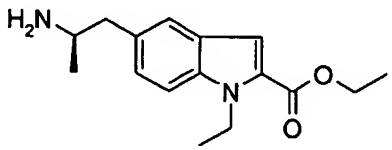


Prepared using the procedure of Preparation **15**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.57-7.45 (7H, m), 7.24 (1H, s), 7.07 (1H, d), 4.68-4.63 (3H, m), 4.40 (2H, q), 3.52-3.44 (1H, m), 3.29-3.25 (1H, m), 2.78-2.72 (1H, m), 1.74 (3H, d), 1.44 (3H, t), 1.37 (3H, t), 1.24 (3H, d) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 379, $[M+Na]^+$ 401.

Preparation 28 : Ethyl 1-ethyl-5-[(2*R*)-2-aminopropyl]-1*H*-indole-2-carboxylate

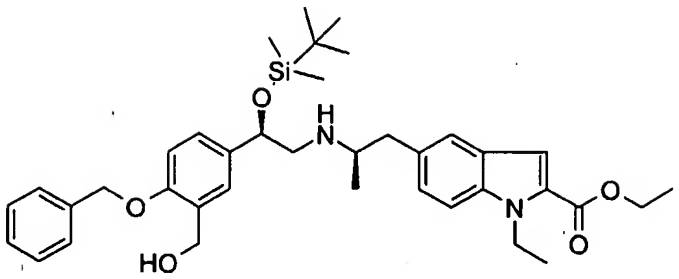


Prepared using the amine from Preparation **27** and the method described for Preparation **14**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.46-7.41 (2H, m), 7.20-7.18 (2H, m), 4.61 (2H, q), 4.35 (2H, q), 3.17-3.09 (1H, m), 2.77-2.64 (2H, m), 1.39 (3H, t), 1.34 (3H, t), 1.10 (3H, d) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 275, $[M+Na]^+$ 297.

Preparation 29 : Ethyl 1-ethyl-5-{(2*R*)-2-[((2*R*)-2-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino]propyl}-1*H*-indole-2-carboxylate

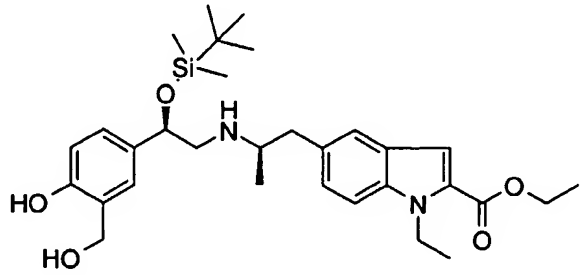


Prepared using the amine from Preparation **28**, and the bromide from preparation **21** and the method described for Preparation **13**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.43-7.29 (8H, m), 7.19 (1H, s), 7.11 (1H, d), 6.99 (1H, d), 6.74 (1H, d), 5.00 (2H, s), 4.73-4.70 (1H, m), 4.61-4.56 (4H, m), 4.30 (2H, q), 3.00-2.88 (2H, m), 2.78-2.61 (3H, m), 1.37-1.31 (6H, m), 1.11 (3H, d), 0.73 (9H, s), -0.08 (3H, s), -0.24 (3H, s) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 645, $[M+Na]^+$ 667.

Preparation 30 : Ethyl 1-ethyl-5-[(2*R*)-2-{{(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylate

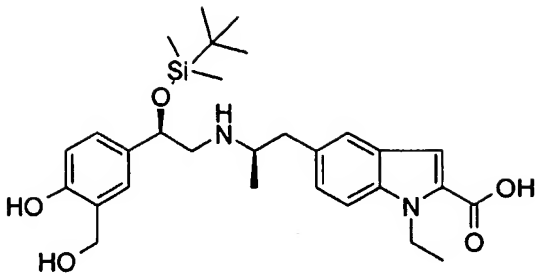


Prepared using the amine from Preparation **29** and the method described for Preparation **12**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.38-7.35 (2H, m), 7.19-7.09 (3H, m), 6.96 (1H, d), 6.64 (1H, d), 4.68-4.58 (5H, m), 4.37 (2H, q), 2.98-2.60 (5H, m), 1.41 (3H, t), 1.36 (3H, t), 1.10 (3H, d), 0.72 (9H, s), -0.09 (3H, s), -0.25 (3H, s) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 555, $[M+Na]^+$ 577.

Preparation 31 : 1-Ethyl-5-[(2*R*)-2-{{(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxylic acid

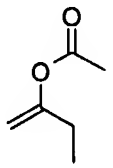


Prepared using the amine from Preparation **30** and the method described for Preparation **11**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.41-7.35 (2H, m), 7.21 (1H, bs), 7.07-6.95 (3H, m), 6.67 (1H, d), 4.94-4.91 (1H, m), 4.60-4.55 (4H, m), 3.54-3.49 (1H, m), 3.09-2.84 (4H, m), 1.27-1.21 (6H, m), 0.67 (9H, s), -0.09 (3H, s), -0.29 (3H, s) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 527, $[M+Na]^+$ 549.

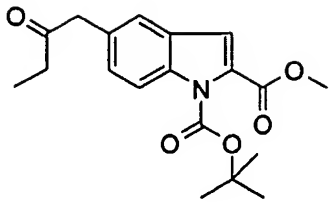
Preparation 32 : Acetic acid 1-methylene-propyl ester



But-1-yne (13.5 g, 0.25 mol) was added to a solution of mercuric acetate (1.2 g, 4.6 mmol) and boron trifluoride dietherate (1.68 g, 11.8 mmol) in acetic anhydride (40 ml) at –10 °C. After stirring for 3 h, the solution was left at –20 °C overnight. The reaction mixture was added to a cooled (0 °C) 6.6 M solution of sodium hydroxide (150 ml). Diethyl ether (150 ml) was then added and the mixture stirred for 1 h. The etheral layer was separated and washed with brine and dried (Na_2SO_4). The product was purified by distillation (120 °C) to yield a clear oil (4.5 g).

^{1}H NMR (400 MHz, CD_3OD) : δ 1.05 (3H, t), 2.18 (3H, s), 2.20 (2H, q), 4.75 (2H, 2xs)

Preparation 33 : 1-*tert*-Butyl 2-methyl 5-(2-oxobutyl)-1*H*-indole-1,2-dicarboxylate

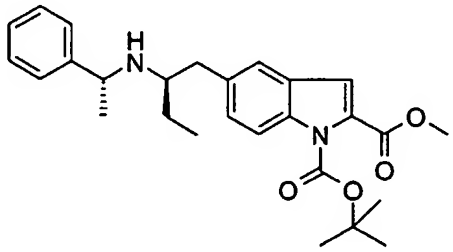


Prepared using the bromide from Preparation **18**, the ester from preparation **32** and the method described for Preparation **17**.

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 8.03 (1H, d), 7.44 (1H, s), 7.25 (1H, d, partially obscured by solvent), 7.05 (1H, s), 3.92 (3H, s), 3.77 (2H, s), 2.48 (2H, q), 1.62 (9H, s), 1.03 (3H, t) ppm.

LRMS (ESI) : m/z $[M+Na]^+$ 368.

Preparation 34 : Methyl 5-{(2*R*)-2-{[(1*R*)-1-phenylethyl]amino}butyl)-1*H*-indole-2-carboxylate

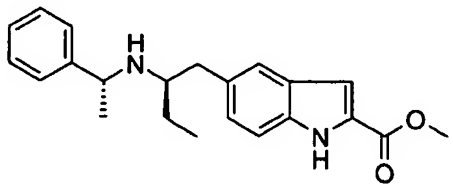


Prepared using the amine from Preparation **33** and the method described for Preparation **16**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 0.81-0.95 (3H, 2xt), 1.27 (3h, 2xd), 1.62 (9H, s), 2.53-2.89 (3H,m), 3.90 (1H, m), 3.92 (3H, 2xs), 6.82-7.20 (4H, m), 7.23-7.29 (4h, m), 7.90 (1H, m) ppm.

LRMS (APCI) : m/z $[M+H]^+$ 451.

Preparation 35 : Methyl 5-{(2*R*)-2-{[(1*R*)-1-phenylethyl]amino}butyl)-1*H*-indole-2-carboxylate

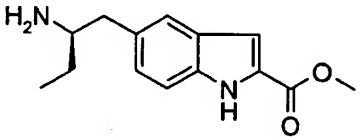


Prepared using the bromide from Preparation **34** and the method described for Preparation **15**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.50-7.41 (7H, m), 7.12 (1H, s), 7.03 (1H, d), 4.43 (1H, q), 3.91 (3H, s), 3.31-3.24 (2H, m), 3.15-3.08 (1H, m), 2.98-2.92 (1H, m), 1.67 (3H, d), 1.66-1.51 (1H, m), 0.9 (3H, t) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 351.

Preparation 36 : Methyl 5-[(2*R*)-2-aminobutyl]-1*H*-indole-2-carboxylate

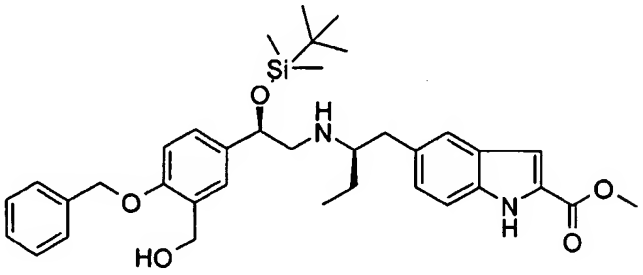


Prepared using the bromide from Preparation **35** and the method described for Preparation **14**.

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 9.39 (1H, bs), 7.49 (1H, s), 7.34 (1H, d), 7.13-7.15 (2H, m), 3.93 (3H, s), 2.99-2.88 (2H, m), 2.55-2.50 (1H, m), 1.51-1.20 (4H, m), 0.99 (3H, t) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 247.

Preparation 37 : Methyl 5-{(2*R*)-2-[((2*R*)-2-[4-(benzyloxy)-3-(hydroxymethyl) phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino] butyl}-1*H*-indole-2-carboxylate



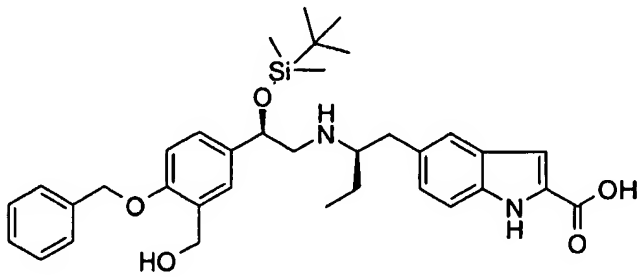
Prepared using the bromide from Preparation **18**, the ester from preparation **36** and the method described for Preparation **13**.

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 8.83 (1H, bs), 7.60-7.50 (6H, m), 7.44 (1H, s), 7.41-7.26 (4H, m), 6.98 (1H, d), 5.25 (2H, s), 4.95-4.85 (3H, m), 4.08 (3H, s),

3.03-2.80 (5H, m), 1.95-1.55 (4H, m), 1.10 (3H, t), 1.01 (9H, s), 0.18 (3H, s), 0.00 (3H, s) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 617.

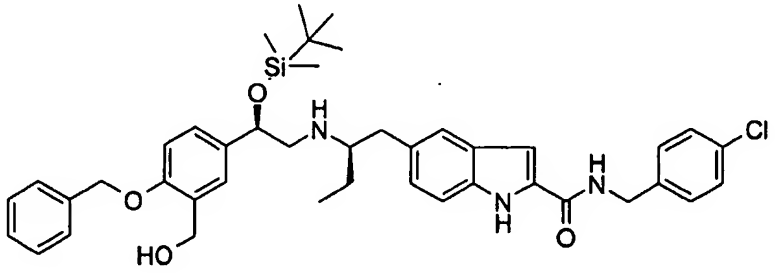
Preparation 38 : 5-{(2*R*)-2-[((2*R*)-2-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino] butyl}-1*H*-indole-2-carboxylic acid



Preparation **37** (790 mg, 1.28 mmol) and LiOH (1 M in water, 2.56 ml) in THF (40 ml) and water (6 ml) were stirred at RT overnight. The solvent was removed *in vacuo* to yield a yellow foam (870 mg).

LRMS (APCI) : m/z $[M+H]^+$ 603.

Preparation 39 : 5-[(2*R*)-2-({(2*R*)- 2-[4-(benzyloxy)-3-(hydroxymethyl) phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}-ethyl}amino)butyl]-*N*-(4-chlorobenzyl)-1H-indole-2-carboxamide

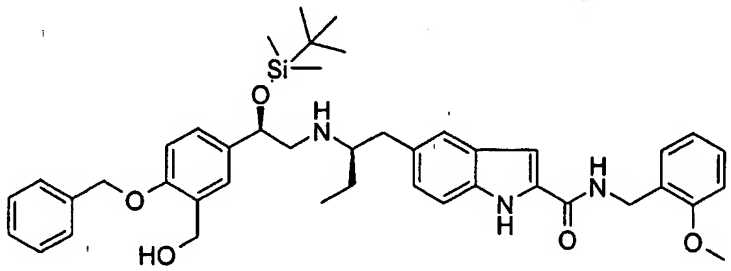


Prepared using the acid from Preparation **38** and the method described for Preparation **1**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.77-7.62 (12H, m), 7.38-7.34 (2H, m), 7.25 (1H, d), 6.99 (1H, d), 5.33 (2H, s), 5.01-5.05 (1H, m), 4.95 (2H, s), 4.85 (2H, s), 3.25-2.95 (5H, m), 2.00-1.65 (2H, m), 1.33 (3H, t), 1.10 (9H, s), 0.28 (3H, s), 0.10 (3H, s) ppm.

LRMS (ESI) : m/z $[M+H]^+$ 726.

Preparation 40 : 5-[(2*R*)-2-({(2*R*)- 2-[4-(benzyloxy)-3-(hydroxymethyl) phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}-ethyl}amino)butyl]-*N*-(2-methoxy benzyl)-1H-indole-2-carboxamide

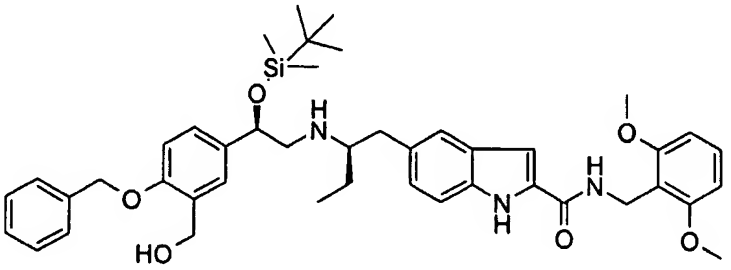


Prepared using the acid from Preparation **38** and the method described for Preparation **1**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.45-7.20 (10H, m), 7.10-6.85 (5H, m), 6.63 (1H, d), 5.00 (2H, s), 4.70 (1H, t), 4.60 (2H, d), 4.55 (2H, s), 3.85 (3H, s), 2.85 (1H, m), 2.75 (2H, m), 2.60 (2H, m), 1.60 (1H, m), 1.40 (1H, m), 1.00 (3H, t), 0.78 (9H, s), -0.05 (3H, s), -0.25 (3H, s).

LRMS (APCI) : m/z $[M+H]^+$ 722.

Preparation 41 : 5-[(2*R*)-2-({(2*R*)- 2-[4-(benzyloxy)-3-(hydroxymethyl) phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}-ethyl}amino)butyl]-*N*-(2,6-dimethoxybenzyl)-1H-indole-2-carboxamide



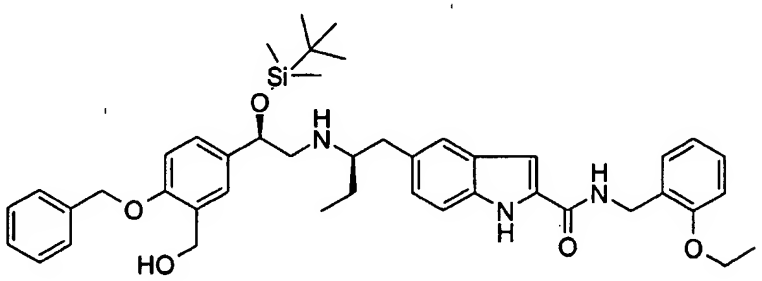
Prepared using the acid from Preparation **38** and the method described for Preparation **1**.

^{1}H NMR (400 MHz, CD_3OD) : Contains δ = 7.50-7.20 (10 H, m), 7.10-6.60 (4H, m), 6.50 (1H, m), 5.00 (2H, s), 4.70 (1H, t), 4.60 (2H, d), 4.55 (2H, s), 3.85 (6H,

s), 2.85 (1H, m), 2.75 (2H, m), 2.60 (2H, m), 1.60 (1H, m), 1.40 (1H, m), 1.00 (3H, t), 0.78 (9H, s), -0.05 (3H, s), -0.25 (3H, s).

LRMS (APCI) : m/z $[M]^+$.752.

Preparation 42 : 5-[(2*R*)-2-({(2*R*)- 2-[4-(benzyloxy)-3-(hydroxymethyl) phenyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}-ethyl}amino)butyl]-*N*-(2-ethoxybenzyl)-1H-indole-2-carboxamide

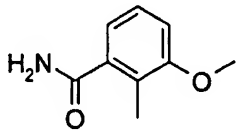


Prepared using the acid from Preparation **38** and the method described for Preparation **1**.

^{1}H NMR (400 MHz, CD_3OD) : δ = 7.45-7.20 (10H, m), 7.10-6.80 (5H, m), 6.63 (1H, d), 4.98 (2H, s), 4.70 (1H, t), 4.60 (2H, d), 4.55 (2H, s), 4.08 (2H, q), 2.85 (1H, m), 2.75 (2H, m), 2.60 (2H, m), 1.60 (1H, m), 1.40 (4H, t, m), 0.98 (3H, t), 0.78 (9H, s), -0.05 (3H, s), -0.25 (3H, s).

LRMS (APCI) : m/z $[M+H]^+$ 736.

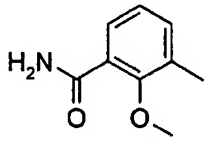
Preparation 43 : 3-Methoxy-2-methylbenzamide



3-Methoxy-2-methylbenzoic acid (5.0 g, 30 mmol) in CH_2Cl_2 (90 ml) and DMF (90 ml) was treated with HOBt (4.06 g, 30 mmol) and WSCDI (5.75 g, 30 mmol) and the resulting mixture stirred at RT for 20 min. After cooling to 0 °C ammonia (2H in EtOH, 30 ml, 60 mmol) was added and the mixture stirred for a further 2 h. The mixture was filtered, the solvent was removed from the filtrate. The crude material was taken up in CH_2Cl_2 and washed with water and brine and dried (Na_2SO_4), which gave a white solid (2.9 g) on isolation.

^{1}H NMR (400 MHz, $DMSO_{d6}$) : δ = 7.62 (1H, s), 7.38 (1H, s), 7.18 (1H, t), 6.98(1H, d) 6.85 (1H, d), 3.80 (3H, s), 2.09 (3H, s).

Preparation 44 : 2-Methoxy-3-methylbenzamide

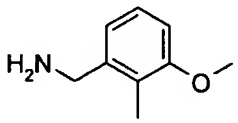


Prepared using 2-methoxy-3-methylbenzoic acid and the method described for Preparation **43**.

^{1}H NMR (400 MHz, $DMSO_{d6}$) : δ = 7.62 (1H, s), 7.42 (1H, s), 7.40 (1H, d), 7.28 (1H, d), 7.01 (1H, t), 3.65 (3H, s), 2.20 (3H, s).

LRMS (ESI) : m/z $[M+Na]^+$ 188.

Preparation 45 : 3-Methoxy-1-methylbenzamine

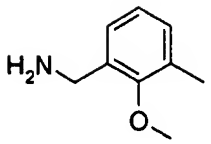


Preparation **44** (2.9 g, 17.5 mmol) in anhydrous THF (30 ml) was heated to 50 °C and BMS ("M in THF, 13 ml 26 mmol) was added dropwise over 40 min. The reaction was then heated to reflux for 4 h and then stirred overnight at RT. The reaction was quenched with 2M HCl (15 ml) and the pH adjusted to < 3. The aqueous phase was washed with CH_2Cl_2 (x2) and then basified with 2M NaOH until ph > 10. The product was extracted with CH_2Cl_2 (2x 100 ml) and dried (Na_2SO_4). On isolation the compounds was a clear oil (506 mg).

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.16 (1H,t), 6.90 (1H,d), 6.75(1H,d), 3.82 (2H, s), 3.80 (3H, s), 2.22 (3H, s), 1.80 (2H, bs)

LRMS (ESI) : m/z $[M+H]^+$ 152.

Preparation 46 : 2-Methoxy-3-methylbenzamine

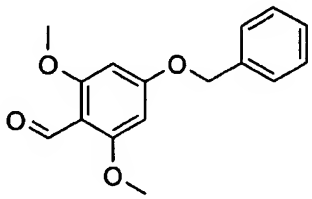


Prepared using Preparation **44** and the method described for Preparation **45**.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.22 (1H, d), 7.20 (1H, d), 6.96(1H, t), 3.90 (2H, s), 3.78 (3H, s), 2.81 (NH2), 2.32 (3H, s)

LRMS (ESI) : m/z $[M+H]^+$ 152

Preparation 47 : 4-Benzyloxy-2,6-dimethoxybenzaldehyde

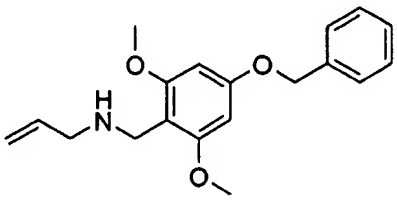


2-6-Dimethoxy-4-hydroxybenzaldehyde (1.83 g, 10 mmol), benzyl bromide (1.71 g, 10 mmol) and anhydrous K_2CO_3 (2.76 g, 20 mmol) in acetonitrile (25 ml) were heated to reflux for 4 h. The reaction mixture was diluted with EtOAc (50 ml) and washed with water (50 ml), brine (50 l) and dried ($MgSO_4$). The crude material was purified by chromatography (0-75 % EtOAc in heptane) to give an off-white colour solid (2.11 g).

^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.86 (6H, s), 5.12 (2H, s), 6.16 (2H, s), 7.37-7.45 (5H, m), 10.36 (1H, s)

LRMS (ESI) : m/z $[M+H]^+$ 273, $[M+Na]^+$ 295

Preparation 48 : Allyl-(4-benzyloxy-2,6-dimethoxybenzyl)amine



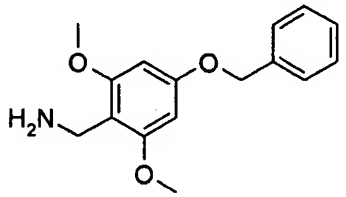
Preparation **47** (1.0 g, 3.68 mmol), allylamine (210 mg, 7.35 mmol), sodium triacetoxyborohydride (779 mg, 7.35 mmol) were stirred at RT in CH_2Cl_2 (25 ml)

16 h. The mixture was diluted with CH_2Cl_2 (50 ml), washed with sat. Na_2CO_3 (2x 50 ml), brine (50 ml) and dried ($MgSO_4$). The product was purified by chromatography (0-5 % MeOH in CH_2Cl_2 with 1 % NH_3) to yield a yellow oil (1.03 g).

^1H NMR (400 MHz, $CDCl_3$) : δ 1.39 (1H, bs), 3.23 (2H, d), 3.78 (6H, s), 3.82 (2H, s), 5.06 (2H, s), 5.13 (2H, dd), 5.95 (1H, m), 6.20 (2H, s), 7.23-7.45 (5H, m)

LRMS (ESI) : m/z $[M+H]^+$ 314.

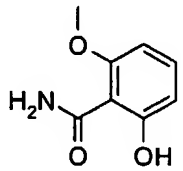
Preparation 49 : 4-Benzyloxy-2,6-dimethoxybenzylamine



Preparation **48** (500 mg, 1.60 mmol) in CH_2Cl_2 (5 ml) was added to a solution of *tetrakis*(triphenylphosphine)palladium(0) (20 mg, 1.60 mmol) and *N,N'*-dimethylbarbituric acid (750 mg, 4.79 (mmol) in CH_2Cl_2 (15 ml) and the mixture heated to 35 °C for 4 h. The mixture was diluted with CH_2Cl_2 (20 ml) and washed with sat. Na_2CO_3 (2x 20 ml) and brine (20 ml) and dried ($MgSO_4$) to leave a yellow oil (529 mg).

LRMS (ESI) : m/z $[M+Na]^+$ 396.

Preparation 50 : 2-Hydroxy-6-methoxybenzamide



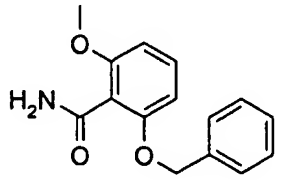
2-hydroxy-6-methoxybenzoic acid (4.0 g, 23.81 mmol) thionyl chloride (10 ml) and DMF (1 drop) were heated to reflux for 2 h. The solvents were removed *in vacuo* and the material taken up inCH_2Cl_2 (25 ml) and cooled < 0 °C. 0.88 Ammonia (3 ml) was added dropwise over 5 min to the mixture and the reaction

stirred overnight at RT. The reaction was diluted with CH_2Cl_2 (incorporating 2 % MeOH) and acidified to pH 2 with 10 % HCl solution, the organics were washed with water and the solvent removed. The crude material was partially purified by chromatography (0-100 % EtOAc in heptane) to leave a white solid (1.54 g).

^{1}H NMR (400 MHz, $DMSO_{d6}$) : δ 3.87 (3H, s), 6.45 (1H, dd), 6.52 (1H, dd), 7.30 (1H, t), 8.10 (1H, bs), 8.16 (1H, bs).

LRMS (ESI) : m/z $[M+H]^+$ 168.

Preparation 51 : 2-benzyloxy-6-methoxybenzamide

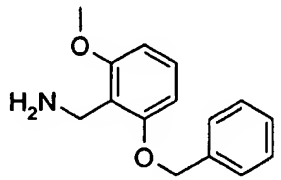


Prepared using Preparation **50** and the method described for Preparation **47**.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.85 (3H, s), 5.12 (2H, s), 5.76 (2H, bs), 6.59 (1H, d), 6.61 (1H, d), 7.28-7.43 (5H, m).

LRMS (ESI) : m/z $[M+H]^+$ 258.

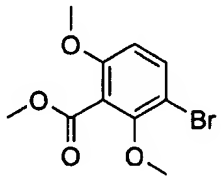
Preparation 52 : 4-Benzyloxy-2,6-dimethoxybenzaldehyde



Lithium aluminiumhydride (1M in Et_2O, 5.21 ml, 5.21 mmol) was added to a solution of Preparation **51** (1.34 g, 5.21 mmol) in THF (20 ml) and the mixture heated to 40 °C for 6 h. The reaction was quenched with (1M NaOH (2 ml) and the mixture stirred at RT for 1 h. The product was extracted with EtOAc (2x 30 ml) and the organics washed with water (50 ml), brine (50 ml) and dried ($MgSO_4$). The product was purified by chromatography (0-5% MeOH inCH_2Cl_2 With 1 % NH_3) to yield a yellow oil (315 mg).

^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.73 (2H, bs), 3.84 (3H, s), 3.90 (1H, s), 5.09 (2H, s), 6.57 (1H, d), 6.61 (1H, d), 7.16 (1H, dd), 7.32-7.44 (5H, m).
LRMS (ESI) : m/z $[M+H]^+$ 244.

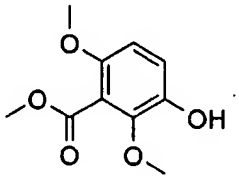
Preparation 53 : Methyl 3-bromo-2,6-dimethoxybenzoate



3-Bromo-2,6-dimethoxybenzoic acid (5.0 g, 19.2 mmol) and thionyl chloride (10 ml) were heated to reflux for 2 h. The mixture was then concentrated *in vacuo* and diluted with CH_2Cl_2 (20 ml) and added to a solution of MeOH (614 mg, 38.4 mmol) and triethylamine (3.88 g, 38.4 mmol) in CH_2Cl_2 (100 ml) at 0 °C. The resulting mixture was allowed to warm to RT and stirred for 64 h. The organics were washed with 10 % HCl (50 ml), brine (50 ml) and dried ($MgSO_4$) and purified by chromatography (0-50 % EtOAC in heptane) to leave a white solid (4.17 g).

^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.82 (3H, s), 3.88 (3H, s), 3.93 (3H, s), 6.61 (1H, d), 7.51 (1H, d).
LRMS (ESI) : m/z $[M+Na]^+$ 299/297.

Preparation 54 : Methyl 2,6-dimethoxy-3-hydroxybenzoate



Preparation **53** (4.16 g 15.1 mmol) in THF (100 ml) was cooled to –78 ° C under nitrogen and treated with butyllithium (1.6 M in hexanes, 10.4 ml, 16.6 mmol). After 10 min at this temp. triisopropylborate (5.69 g, 20.3 mmol) was added and the mixture allowed to warm to RT over 1h and stirred for a further 2 h. The reaction was quenched with 2M HCl (20 ml) and the solution stirred at

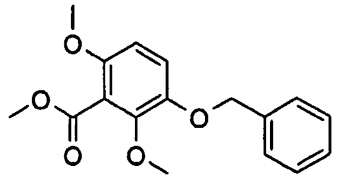
RT for 20 h. The product was extracted with EtOAc (2 x 100 ml), washed with brine (100 ml) and dried ($MgSO_4$) to leave a brown oil (3.80 g).

The crude material was diluted with THF (20 ml) and hydrogen peroxide (100 vol., 4 ml) and the resulting mixture heated to reflux for 20 h. EtOAc (50 ml) was added and the organics washed with 10 % ammonium iron (III) sulfate until no more colour change, then washed with brine (50 ml) before being dried ($MgSO_4$). The product was purified by chromatography (0-50 % EtOAc in heptane) (1.03 g).

^1H NMR (400 MHz, $CDCl_3$) : δ 3.78 (3H, s), 3.89 (3H, s), 3.95 (3H, s), 6.60 (1H, d), 6.95 (1H, d), 5.07 (1H, bs).

LRMS (ESI) : m/z $[M+Na]^+$ 235.

Preparation 55 : Methyl 3-benzyloxy-2,6-dimethoxybenzoate

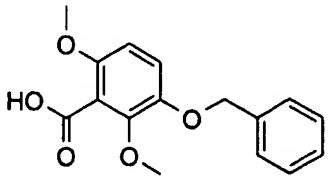


Prepared using Preparation **54** and the method described for Preparation **47**.

^1H NMR (400 MHz, $CDCl_3$) : δ 3.78 (3H, s), 3.92 (3H, S), 3.93 (3H, s), 5.08 (2H, s), 6.57 (1H, d), 6.90 (1H, d), 7.28-7.42 (5H, m)

LRMS (ESI) : m/z $[M+Na]^+$ 325.

Preparation 56 : 3-Benzyloxy-2,6-dimethoxybenzoic acid



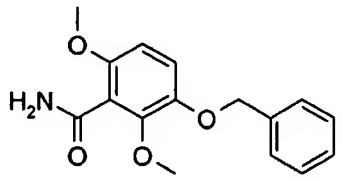
Preparation **55** (870 mg, 2.89 mmol) and NaOH (230 mg, 5.76 mmol) in a mixture of THF (10 ml) and water (2 ml) were heated to reflux for 2 days. The solvent was removed and the material acidified to pH 2 with 10 % HCl. The acid was extracted with EtOAc (100 ml) and washed with brine (100 ml) and

dried ($MgSO_4$). The resulting solids were slurried in hexane and filtered to leave a cream colour solid (536 mg).

^1H NMR (400 MHz, $DMSO_{d6}$) : δ 3.69 (3H, s), 3.75 (3H, s), 5.08 (2H, s), 6.70 (1H, d), 7.07 (1H, d), 7.29-7.45 (5H, m).

LRMS (ESI) : m/z $[M-H]^-$ 287.

Preparation 57 : 3-Benzyloxy-2,6-dimethoxybenzamide

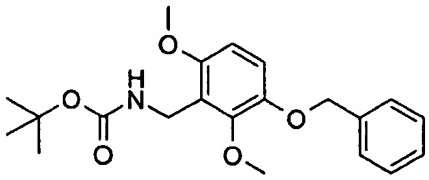


Prepared using Preparation **56** and the method described for Preparation **1**.

^1H NMR (400 MHz, $DMSO_{d6}$) : δ 3.67 (3H, s), 3.75 (3H, s), 5.06 (2H, s), 6.66 (1H, d), 7.02 (1H, d), 7.31-7.46 (5H, m), 7.25 (1H, bs), 7.56 (1H, bs).

LRMS (ESI) : m/z $[M+Na]^+$ 310.

Preparation 58 : (3-Benzyloxy-2,6-dimethoxy-benzyl)-carbamic acid *tert*-butyl ester



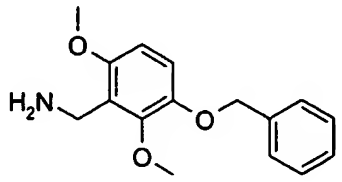
Preparation **57** (277 mg, 965 μmol) and BMS (2M in THF, 0.97 ml, 1.93 mmol) in THF (10 ml) were heated to reflux for 20 min. MeOH (5 ml) was added followed by cHCl (0.2 ml) and the resulting mixture heated for a further 1 h. The solvents were removed and the crude product triturated with Et_2O to leave a white solid (277 mg). This solid was taken up in a mixture of dioxane (10 ml) and water (1ml) and treated with di-*tert*-butyloxydicarbonate (325 mg, 10.6 mmol) and sodium hydrogen carbonate (162 mg, 10.6 mmol) and the resulting mixture stirred at RT for 4 h. The mixture was diluted with EtOAc (25 ml) and washed with brine (50 ml) and dried ($MgSO_4$) to leave a light brown coloured oil

(427 mg). This crude material was taken up in acetone (10 ml) and treated with iodomethane (71 mg, 500 μmol) and anhydrous potassium carbonate (266 mg, 1.93 mmol) and heated to reflux for 16 h. A further aliquot of iodomethane (71 mg, 500 μmol) was added and heating continued for a further 2 h. The reaction was quenched with water (20 ml) and the product extracted with EtOAc (2x 50 ml). The organics were washed with brine and dried ($MgSO_4$) and the crude material purified by chromatography (0-30 % EtOAc in heptane) to yield a clear oil (212 mg).

^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.44 (9H, s), 3.79 (3H, s), 3.91 (3H, s), 4.42 (2H, d), 5.05 (3H, s), 6.52 (1H, d), 6.83 (1H, d), 7.31-7.45 (5H, m).

LRMS (ESI) : m/z $[M+Na]^+$ 396.

Preparation 59 : 3-Benzyloxy-2,6-dimethoxybenzylamie hydrochloride



Preparation **58** (212 mg, 568 μmol) in dioxane (5 ml) was treated with HCl (4M in dioxane, 1.0 ml) and the solution stirred at RT for 2 h and at 60 °C for 2 h. the solvent was removed *in vacuo* to yield a white solid (160 mg).

^{1}H NMR (400 MHz, $DMSO_{d6}$) : δ 3.76 (3H, s), 3.83 (3H, s), 3.93 (2H, bs), 5.09 (2H, s), 6.74 (1H, d), 7.13 (1H, d), 7.32-7.46 (5H, m), 7.98 (3H, bs).

LRMS (ESI) : m/z $[M+H]^+$ 274.

***In vitro* activity of the indole derivatives of formula (1)**

The ability of the indole derivatives of the formula (1) to act as potent β2 agonists therefore mediating smooth muscle relaxation may be determined by the measure of the effect of beta-2 adrenergic receptor stimulation on electrical field stimulated-contraction of guinea pig trachea strips.

Guinea-pig trachea

Male, Dunkin-Hartley guinea pigs (475-525g) are killed by CO_2 asphyxiation and exsanguination from the femoral artery and the trachea is isolated. Four preparations are obtained from each animal, starting the dissection immediately below the larynx and taking 2.5 cm length of trachea. The piece of trachea is opened by cutting the cartilage opposite the trachealis muscle, then transverse sections, 3-4 cartilage rings wide, are cut. The resulting strip preparations are suspended in 5 ml organ baths using cotton threads tied through the upper and lower cartilage bands. The strips are equilibrated, un-tensioned, for 20 minutes in a modified Krebs Ringer buffer (Sigma K0507) containing 3 μM Indomethacin (Sigma I7378), 10 μM Guanethidine (Sigma G8520) and 10 μM Atenolol (Sigma A7655), heated at 37°C and gassed with 95% O_2/5% CO_2, before applying an initial tension of 1 g. The preparations are allowed to equilibrate for a further 30-45 minutes, during which time they are re-tensioned (to 1 g) twice at 15-minute intervals. Changes in tension are recorded and monitored via standard isometric transducers coupled to a data-collection system (custom-designed at Pfizer). Following the tensioning equilibration, the tissues are subjected to electrical field stimulation (EFS) using the following parameters : 10 s trains every 2 minutes, 0.1 ms pulse width, 10 Hz and just-maximal voltage (25 Volts) continuously throughout the length of the experiment. EFS of post-ganglionic cholinergic nerves in the trachea results in monophasic contractions of the smooth muscle and twitch height is recorded. The organ baths are constantly perfused with the above-described Krebs Ringer buffer by means of a peristaltic pump system (pump flow rate 7.5 ml / minute) throughout the experiment, with the exception of when a beta-2 agonist according to the present invention is added, the pump is then stopped for the time of the

cumulative dosing to the bath and started again after maximal response is reached for the wash-out period.

Experimental protocol for assessment of potency and efficacy

Following equilibration to EFS, the peristaltic pump is stopped and the preparations 'primed' with a single dose of 300 nM isoprenaline (Sigma I5627) to establish a maximal response in terms of inhibition of the contractile EFS response. The isoprenaline is then washed out over a period of 40 minutes. Following the priming and wash-out recovery, a standard curve to isoprenaline is carried out on all tissues (Isoprenaline Curve 1) by means of cumulative, bolus addition to the bath using half log increments in concentration. The concentration range used is 1^{e-9} to $1^{e}/3^{e-6}$ M. At the end of the isoprenaline curve the preparations are washed again for 40 minutes before commencing a second curve, either to isoprenaline (as internal control) or a beta-2 agonist according to the present invention. Beta-2 agonist responses are expressed as percentage inhibition of the EFS response. Data for beta-2 agonist are normalised by expressing inhibition as a percentage of the maximal inhibition induced by isoprenaline in Curve 1. The EC_{50} value for beta-2 agonist according to the present invention refers to the concentration of compound required to produce half maximal effect. Data for beta-2 agonists according to the present invention are then expressed as relative potency to isoprenaline defined by the ratio (EC_{50} beta-2 agonist)/(EC50 Isoprenaline).

Confirmation of beta-2 mediated functional activity

Beta-2 agonist activity of test compounds is confirmed using the protocol above, however, prior to constructing the curve to beta-2 agonist according to the present invention, the preparations are pre-incubated (for a minimum of 45 minutes) with 300 nM ICI 118551 (a selective β_2 antagonist) which results in the case of a beta-2 mediated effect in a rightward-shift of the test compound dose response curve.

It has thus been found that the indole derivatives of formula (1) according to the present invention that have been tested show a relative potency to Isoprenaline which is comprised between 0.008 and 2.0.

According to another alternative, the agonist potency for the β2 receptor of the indole derivatives of the formula (1) may also be determined by the measure of the concentration of compound according to the present invention required to produce half maximal effect (EC_{50}) for the β2 receptor.

Compound Preparation

10 mM/100% DMSO (dimethylsulfoxide) stock of compound is diluted to required top dose in 4 % DMSO. This top dose is used to construct a 10-point semi-log dilution curve, all in 4 % DMSO. Isoprenaline (Sigma, I-5627) was used as a standard in every experiment and for control wells on each plate. Data was expressed as % Isoprenaline response.

Cell Culture

CHO (Chinese Hamster Ovary) cells recombinantly expressing the human β2 adrenergic receptor (from Kobilka et al., PNAS 84: 46-50, 1987 and Bouvier et al., Mol Pharmacol 33: 133-139 1988 CHOhβ2) were grown in Dulbeccos MEM/ NUT MIX F12 (Gibco, 21331-020) supplemented with 10 % foetal bovine serum (Sigma, F4135, Lot 90K8404 Exp 09/04), 2 mM glutamine (Sigma, G7513), 500 µg/ml geneticin (Sigma, G7034) and 10 µg/ml puromycin (Sigma, P8833). Cells were seeded to give about 90 % confluency for testing.

Assay Method

25 µl / well each dose of compound was transferred into a cAMP- Flashplate® (NEN, SMP004B), with 1% DMSO as basal controls and 100 nM Isoprenaline as max controls. This was diluted 1:2 by the addition of 25 µl / well PBS. Cells were trypsinised (0.25% Sigma, T4049), washed with PBS (Gibco, 14040-174) and resuspended in stimulation buffer (NEN, SMP004B) to give $1x10^6$ cells / ml CHOhB2. Compounds were incubated with 50 µl / well cells for 1 hour. Cells were then lysed by the addition of 100 µl / well detection buffer (NEN,

SMP004B) containing 0.18 µCi / ml ^{125}I-cAMP (NEN, NEX-130) and plates were incubated at room temperature for a further 2 hours. The amount of ^{125}I-cAMP bound to the Flashplate® was quantified using a Topcount NXT (Packard), normal counting efficiency for 1 minute. Dose-response data was expressed as % Isoprenaline activity and fitted using a four parameter sigmoid fit.

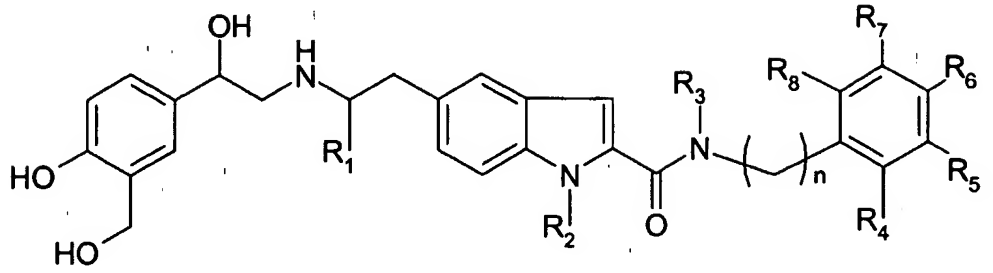
It has thus been found that the indole derivatives of formula (1) according to the present invention that are illustrated in examples 1 to 36 above show a β2 cAMP EC_{50} between 0.02 nM and 4 nM.

The below results illustrate the activity of the compounds of formula (1):

Example Number	Cell based cAMP β2 activity (nM)
1	0.02
2	0.80
3	0.05
4	0.12
9	0.02
22	0.02
29	3.99
36	0.38

CLAIMS

1. A compound of the formula (1) :



(1)

wherein

- n is an integer equal to 0, 1, 2, 3 or 4;
- R_1 and R_2 are each independently selected from hydrogen and (C_1-C_4)alkyl;
- R_3 is selected from the group consisting of hydrogen or (C_1-C_6)alkyl optionally substituted by a hydroxy; and
- R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, benzyloxy, hydroxy(C_1-C_6)alkyl, thio(C_1-C_6)alkyl, halo and trifluoromethyl,

or a pharmaceutically acceptable salt and/or isomer, tautomer, solvate or isotopic variation thereof.

2. A compound according to claim 1 wherein

- n is 1 or 2;
- R_1 is a (C_1-C_4)alkyl;
- R_2 is selected from hydrogen and (C_1-C_4)alkyl;
- R_3 is selected from hydrogen and (C_1-C_6)alkyl; and
- R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, benzyloxy, hydroxy(C_1-C_6)alkyl, thio(C_1-C_6)alkyl, halo and trifluoromethyl,

or a pharmaceutically acceptable salt and/or isomer, tautomer, solvate or isotopic variation thereof.

3. A compound according to claim 1 wherein

- n is an integer equal to 1 or 2;
- R_1 is selected from methyl and ethyl
- R_2 is selected from hydrogen, methyl and ethyl;
- R_3 is selected from hydrogen and methyl; and
- R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, benzyloxy, hydroxy(C_1-C_6)alkyl, thio(C_1-C_6)alkyl, halo and trifluoromethyl,

or a pharmaceutically acceptable salt and/or isomer, tautomer, solvate or isotopic variation thereof.

4. A compound according to claim 1 wherein

- n is an integer equal to 1 or 2;
- R_1 is selected from methyl and ethyl
- R_2 is selected from hydrogen, methyl and ethyl;
- R_3 is selected from hydrogen or methyl; and
- R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, hydroxy, methyl, methoxy, ethoxy, benzyloxy, thiomethyl, halo and trifluoromethyl,

or a pharmaceutically acceptable salt and/or isomer, tautomer, solvate or isotopic variation thereof.

5. A compound according to any one of claims 1 to 4, wherein at least 2 of R_4, R_5, R_6, R_7 and R_8 are hydrogen.

6. A compound according to claim 1 wherein n is equal to 1 or 2, R_1 is methyl, R_2 and R_3 are hydrogen atoms, and R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, Hydroxy(C_1-C_6)alkyl, thio(C_1-C_6)alkyl, halo and trifluoromethyl,

or a pharmaceutically acceptable salt and/or isomer, tautomer, solvate or isotopic variation thereof.

7. A compound according to claim 1 wherein n is equal to 1, R_1 is methyl, R_2 and R_3 are hydrogen atoms, and R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, thio$(C_1$-$C_6)$alkyl and trifluoromethyl,

or a pharmaceutically acceptable salt and/or isomer, tautomer, solvate or isotopic variation thereof.

8. A compound according to claim 1 wherein n is equal to 1, R_1 is methyl, R_2 and R_3 are hydrogen atoms, and R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy and trifluoromethyl, provided that at least 2 of R_4, R_5, R_6, R_7 and R_8 are hydrogen,

or a pharmaceutically acceptable salt and/or isomer, tautomer, solvate or isotopic variation thereof.

9. A compound according to claim 1 wherein n is equal to 1, R_1 is methyl, R_2 and R_3 are hydrogen atoms, and R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen, methyl, methoxy and trifluoromethyl provided that at least 2 of R_4, R_5, R_6, R_7 and R_8 are hydrogen,

or a pharmaceutically acceptable salt and/or isomer, tautomer, solvate or isotopic variation thereof.

10. A compound according to claim 1 selected from the group consisting of :
5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino) propyl]-*N*-(2-methoxybenzyl)-1*H*-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl} amino) propyl]-*N*-[4-(trifluoromethyl)benzyl]-1*H*-indole-2-carboxamide,
N-(2,6-dimethoxybenzyl)-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxy-methyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino) propyl]-*N*-(3-methoxybenzyl)-1*H*-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino) propyl]-*N*-[2-(3-methoxyphenyl)ethyl]-1*H*-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(2,4-dichlorobenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(3-hydroxy-2,6-dimethoxybenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-benzyloxy-3-hydroxy methyl phenyl)ethyl} amino)propyl}-*N*-(2-benzyloxy-6-methoxybenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(4-hydroxy-2,6-dimethoxybenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-benzyloxy-6-methoxybenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-hydroxy-6-methoxybenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2,6-difluorobenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-chlorobenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-fluorobenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(4-hydroxybenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(3-hydroxybenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-methylsulfanylbenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(4-methylsulfanylbenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2,3-dimethoxybenzyl)-1H-indole-2-carboxamide,

5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2,4-dimethoxybenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-ethoxybenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-benzyl-*N*-methyl-1H-indole-2-carboxamide,
[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-benzyl-1H-indole-2-carboxamide,
[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(4-fluorobenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(2-methoxy-3-methyl-benzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) propyl}-*N*-(3-methoxy-2-methylbenzyl)-1H-indole-2-carboxamide,
1-Ethyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl} amino)propyl}-*N*-(2,6-dimethoxybenzyl)-1H-indole-2-carboxamide,
1-Ethyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl} amino)propyl}-*N*-(2-ethoxybenzyl)-1H-indole-2-carboxamide,
1-Ethyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl} amino)propyl}-*N*-(4-chlorobenzyl)-1H-indole-2-carboxamide,
1-Methyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl} amino)propyl}-*N*-(2,6-dimethoxybenzyl)-1H-indole-2-carboxamide,
1-Methyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl} amino)propyl}-*N*-(2-methoxybenzyl)-1H-indole-2-carboxamide,
1-Methyl-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxy methylphenyl)ethyl} amino)propyl}-*N*-(4-chlorobenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) butyl}-*N*-(2-methoxybenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) butyl}-*N*-(2,6-dimethoxybenzyl)-1H-indole-2-carboxamide,
5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) butyl}-*N*-(2-ethoxybenzyl)-1H-indole-2-carboxamide, and,

11. A compound according to claim 10, said compound being 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino) butyl}-*N*-benzyl-1H-indole-2-carboxamide.

12. A compound according to claim 10, said compound being 5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino)propyl]-*N*-(2-methoxybenzyl)-1*H*-indole-2-carboxamide,

13. A compound according to claim 10, said compound being *N*-(2,6-dimethoxybenzyl)-5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)propyl]-1*H*-indole-2-carboxamide,

14. A compound according to claim 10, said compound being 5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino)propyl]-*N*-(3-methoxybenzyl)-1*H*-indole-2-carboxamide,

15. A compound according to claim 10, said compound being 5-[(2*R*)-2-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino)propyl]-*N*-[2-(3-methoxyphenyl)ethyl]-1*H*-indole-2-carboxamide, and,

16. A compound according to claim 10, said compound being 5-[(2*R*)-2-({(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl phenyl)ethyl}amino)propyl}-*N*-(3-hydroxy-2,6-dimethoxybenzyl)-1H-indole-2-carboxamide.

17. A pharmaceutical composition including a compound of the formula (1) as described in claim 1 or a pharmaceutically acceptable salt or derived form thereof, together with customary pharmaceutically innocuous excipients and/or additives.

18. A compound of the formula (1) as described in claim 1 or a pharmaceutically acceptable salt, derived form or composition thereof, for use as a medicament.

19. A compound of the formula (1) as described in claim 1 or a pharmaceutically acceptable salt, derived form or composition thereof, for use

in the treatment of diseases, disorders, and conditions in which the β2 receptor is involved.

20. A compound of the formula (1) as described in claim 1 or a pharmaceutically acceptable salt, derived form or composition thereof, for use in the treatment of diseases, disorders, and conditions selected from the group consisting of :

- asthma of whatever type, etiology, or pathogenesis, in particular asthma that is a member selected from the group consisting of atopic asthma, non-atopic asthma, allergic asthma, atopic bronchial IgE-mediated asthma, bronchial asthma, essential asthma, true asthma, intrinsic asthma caused by pathophysiologic disturbances, extrinsic asthma caused by environmental factors, essential asthma of unknown or inapparent cause, non-atopic asthma, bronchitic asthma, emphysematous asthma, exercise-induced asthma, allergen induced asthma, cold air induced asthma, occupational asthma, infective asthma caused by bacterial, fungal, protozoal, or viral infection, non-allergic asthma, incipient asthma, wheezy infant syndrome and bronchiolytis,

- chronic or acute bronchoconstriction, chronic bronchitis, small airways obstruction, and emphysema,

- obstructive or inflammatory airways diseases of whatever type, etiology, or pathogenesis, in particular an obstructive or inflammatory airways disease that is a member selected from the group consisting of chronic eosinophilic pneumonia, chronic obstructive pulmonary disease (COPD), COPD that includes chronic bronchitis, pulmonary emphysema or dyspnea associated or not associated with COPD, COPD that is characterized by irreversible, progressive airways obstruction, adult respiratory distress syndrome (ARDS), exacerbation of airways hyper-reactivity consequent to other drug therapy and airways disease that is associated with pulmonary hypertension,

- bronchitis of whatever type, etiology, or pathogenesis, in particular bronchitis that is a member selected from the group consisting of acute bronchitis, acute laryngotracheal bronchitis, arachidic bronchitis, catarrhal bronchitis, croupus bronchitis, dry bronchitis, infectious asthmatic bronchitis, productive bronchitis, staphylococcus or streptococcal bronchitis and vesicular bronchitis,

- bronchiectasis of whatever type, etiology, or pathogenesis, in particular bronchiectasis that is a member selected from the group consisting of cylindric bronchiectasis, sacculated bronchiectasis, fusiform bronchiectasis, capillary bronchiectasis, cystic bronchiectasis, dry bronchiectasis and follicular bronchiectasis.

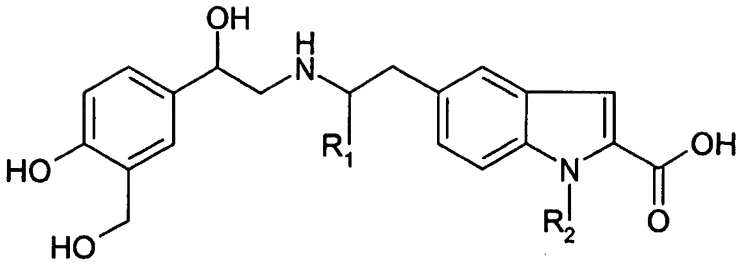
21. The use of a compound of the formula (1) as described in claim 1 or of a pharmaceutically acceptable salt, derived form or composition thereof, for the manufacture of a drug having a β2 agonist activity.

22. The use of a compound of the formula (1) as described in claim 1 or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a drug for the treatment of diseases, disorders, and conditions selected from the group as described in claim 16.

23. A method of treatment of a mammal, including a human being, with a β2 agonist including treating said mammal with an effective amount of a compound of the formula (1) as described in claim 1 or with a pharmaceutically acceptable salt, derived form or composition thereof.

24. A method according to claim 19 where the disease, disorder or condition is selected from the group as described in claim 16.

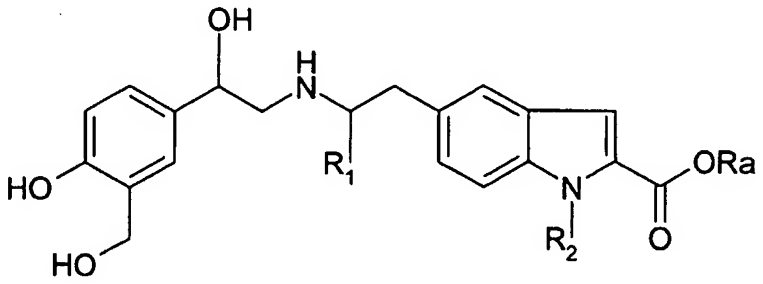
25. An intermediate of formula (2):



(2)

wherein R_1 and R_2 are each independently selected from hydrogen and (C_1-C_4)alkyl.

26. An intermediate of formula (4):



(4)

wherein R_1 and R_2 are each independently selected from hydrogen and (C_1-C_4)alkyl, and Ra is a suitable acid protecting group selected from (C_1-C_4)alkyl groups.

INTERNATIONAL SEARCH REPORT

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PCT/IB 03/04441

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/40 C07D209/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0 822 185 A (PFIZER) 4 February 1998 (1998-02-04) cited in the application the whole document	1-26
A	WO 94 29290 A (PFIZER ;DOW ROBERT L (US); WRIGHT STEPHEN W (US)) 22 December 1994 (1994-12-22) the whole document	1-26

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 January 2004	20/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Von Daacke, A

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